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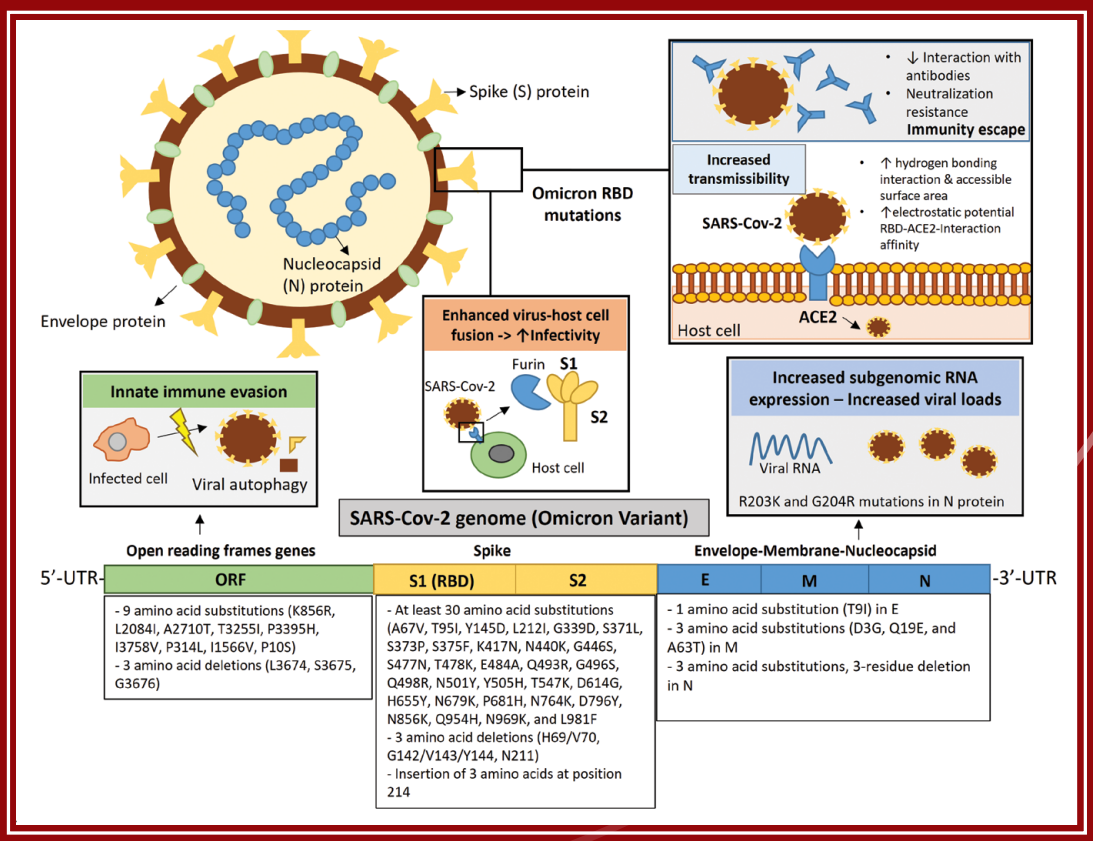

The genetic profile of the Omicron variant and its implications for the viral properties of SARS-CoV-2

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Dear colleagues,

In the current issue, the editorial by Tzakis et al. describes in detail the operation of uterus transplantation, from the original concept up to human trials through a very interesting personal experience. The editorial by Tourkochristou et al. provides the latest information on the new SARS-CoV-2 variant of concern Omicron, including its genetic profile, its characteristics, and its impact on the immune system and vaccination against COVID-19.

The original article by Merekoulias et al. investigates the outbreak of COVID-19 cases in a rehabilitation center and examines the evidence on the preventive effect of vaccination. In addition, this study evaluates the association between viral load and severity of COVID-19 disease. Moreover, this issue includes the review by Kitsou et al. on the management of the COVID-19 pandemic, focusing on management guidelines and the actions taken in the Radiation Oncology Department within a tertiary public Hospital. The review, by Papantoniou et al. presents important elements on primary colorectal cancer prevention and the role of primary care physicians in this setting.

Lastly, this issue includes a case report by Bousis et al. which depicts an unusual case of tuberculosis in a 27-years old male, previously healthy, who was presented with a solid neck mass without any other associated features of the disease, highlighting the need for clinicians to include tuberculosis in the differential diagnosis of cervical lymphadenopathy.

Yours sincerely

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A journey through uncharted waters: Uterus Transplants (UTx)

Andreas G Tzakis

INTRODUCTION

Transplantation of the uterus (UTx) concluded the list of the viscera to be successfully transplanted in humans. The first fully reported UTx took place from a deceased donor in humans in 2011 in Antalya, Turkey [1] and from a live donor in 2013 in Sweden [2,3].

Why did it take so long?

The uterus is not a vital organ and consequently transplantation could not be attempted until safe and effective immunosuppression was established with vital organ transplants. Moreover, contrary to the other transplanted viscera, the uterus is within the realm of gynecology and not general surgery or urology, the specialties of most abdominal transplant surgeons. Gynecologists typically do not perform transplants.

My interest in these transplants was planted 15 years ago. I was inspired by a young woman who underwent a multivisceral transplant (Liver, Stomach, Pancreas, Intestine) at our program but was still not "whole": she had a prior hysterectomy and could not bear children...

Would a transplant of the uterus have been possible? How many other patients could benefit from this procedure? I began to look into these questions.

I found out that there are thousands of women of reproductive age who do not have a uterus and suffer from "uterine factor infertility". In addition to surgical hysterectomies, 1 in 5000 women are born without a uterus (MRKH syndrome). In the US their number is estimated at 50.000. In Greece this number is likely 1500-2000. These are otherwise healthy women who have normal ovaries and a vagina which is usually underdeveloped.

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Until now, they could have children only by adoption or surrogacy, two choices that have helped many women fulfill their dreams. Unfortunately, these are not viable options for many women because of personal, cultural, religious, and legal reasons which are prohibitive.

In addition, a uterus transplant is the only option that gives the woman the opportunity to carry the responsibility, pain and joy of bearing and giving birth to her child, a child with her genetic signature.

For these reasons I started exploring the feasibility of UTx.

Looking at existing experimental models, Brannstrom and his associates had shown that uterine transplants are feasible in small animals and could produce healthy offspring [4]. Positive results in small animals may not always be transferable to large animals, let alone humans.

The next question was whether we could reproduce these results in large animals? My associates Drs Akin Tekin, Tom De Faria and Takis Tryphonopoulos, a very committed group of surgeons, worked diligently with me.

In choosing an appropriate large animal model, one has to consider that the reproductive system is species specific. The one closest to humans, anatomically and physiologically, is the reproductive system of the primates.

Experiments with primates are limited by very strict regulations and high cost.

In addition, effective immunosuppression has been problematic and requires extremely high doses which can be toxic [5]. Baboons find creative ways to get rid of the pills, consequently the medications must be administered parenterally. In addition, experiments are emotionally difficult to perform because of the humanoid features of these animals.

Our initial objective was to test whether we could

Key words: *Transplant; Uterus Transplantation*

establish, long term, the viability of the laboratory animals bearing healthy uterine grafts. We wanted to study rejections and response to treatment. We started with MHC defined mini-Swine, a model with an established record in Transplantation. Dr David Sachs was kind enough to provide the animals.

All our experiments were done with the preconceived notion that if successful, we planned to use deceased donors in humans. This allowed us the liberal use of donor tissues without limitations related to postoperative donor survival. All donors were euthanized after donation.

We developed a heterotopic model [6]: we used the uterine graft attached to a vaginal cuff en block with their vascular pedicle. The latter included the donor uterine, iliac vessels, the abdominal aorta, the corresponding veins and the inferior vena cava.

The operation was extraperitoneal. The abdominal aorta and inferior vena cava of the donor were anastomosed to the lower abdominal vessels of the recipient, much like a kidney transplant. We exteriorized the donor vagina, just like an ileostomy, in order to have easy access to the graft which could be assessed visually every day. Hysteroscopies and biopsies could be performed with simple sedation (Figure 1).

Immunosuppression was based on Tacrolimus and Steroids.

The biologic behavior of the uterus proved to be similar to the kidney allografts. We learned that the uterine allografts in the mini swine develop rejections which are reversible with the standard regimens. Long term survival with a healthy uterine allograft was possible!

At that time, we moved to primates housed in the Mannheimer foundation, an outstanding primate facility near Miami.

The baboons are very curious animals. If we exteriorized the vagina, they were certain to chew on it and cause fatal bleeding. For this reason, we performed a hysterectomy and placed the transplant orthotopically. We anastomosed the pedicles of the abdominal aorta and inferior vena cava of the donor to the corresponding vessels of the recipient. The donor vagina was anastomosed to the vagina of the recipient. Follow up of the uterine graft was performed with hysteroscopies which had to take place under general anesthesia [7] (Figure 2).

A fortuitous coincidence was that at that time I received an Honorary Degree at the University of Gothenburg and had the opportunity to meet the Swedish team. They were performing uterine autotransplants in baboons [8]. These had to be performed in a WHO approved facility in Nairobi, Kenya because of severe regulatory restrictions in Sweden. They invited me to participate!

I gladly did that and subsequently invited them to work with us at the Mannheimer Foundation.

The Swedish group had a primary focus on living related donors in humans, so the animal transplants in Nairobi were autotransplants and imitated transplants from a living donor.

The Transplants in Florida were allografts: the donor was euthanized after donation, the transplant imitated UTx from a deceased donor.

There are some very important technical differences between the 2 kinds of transplants.

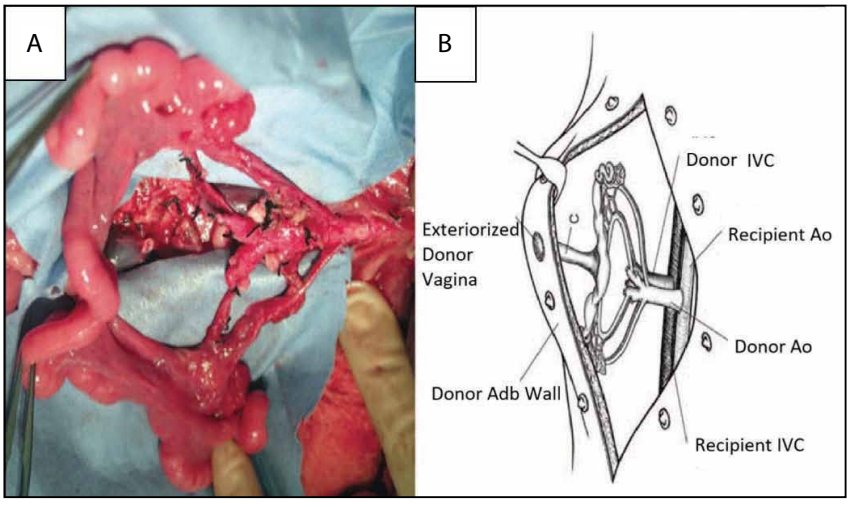

Figure 1. Heterotopic Uterus Transplantation in Mini Swine. Note that the Uterus bares little resemblance to the human uterus. The donor Aorta and IVC are anastomosed end to the side to the recipient aorta and IVC. The donor vagina is exteriorized for easy access.

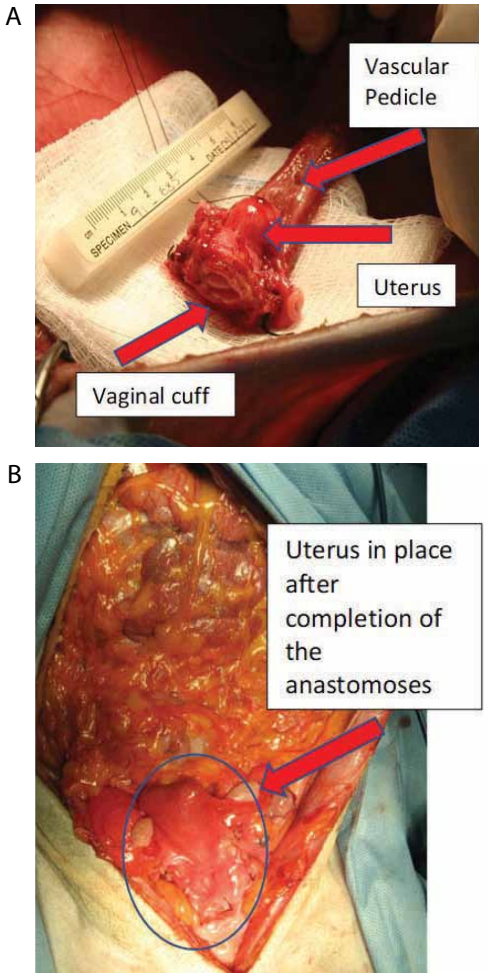

Figure 2. Uterus transplant in a baboon. 2a: the graft after reperfusion 2b: The graft before closure of the abdomen.

In the autotransplants, the blood inflow is from the Uterine artery and outflow through the Uterine vein. These vessels are very small and thin, particularly in the baboons. They need to be dissected without damage. Anastomoses are very delicate.

In the transplants we performed in Florida, the vascular anastomoses were performed with the more robust aorta and IVC.

All baboons survived the surgery and postoperative course. From the experiments in Florida, only one survived long term with a healthy uterus graft. The others had to be euthanized [n=3] due to weight loss, one lost her graft to rejection due to inadequate immunosuppression.

How are these techniques relevant to human transplantation?

In the human living donor model, the internal iliac artery and its major branches have to be preserved or there is a risk of severe pelvic ischemia. Arterial inflow is through the uterine arteries and venous outflow by the uterine veins. These vessels, particularly the uterine vein, are wrapped around the ureters of the donor and must be freed from the ureters intact. The required dissection is very delicate and is performed with diathermy for the most part. It may result in damage of the ureters directly or indirectly by destroying their blood supply.

In the deceased donor model, the vital organs are removed first. The abdominal aorta, IVC, common and external iliac vessels are included with the vital organs which are recovered contemporaneously and cannot be used for the UTx.

In angiograms we performed ex vivo in resected human uteri, we found that there is a vascular venous plexus within the broad ligament which could be damaged when skeletonized.

As a consequence, the uterine graft is recovered with the internal iliac vessels and their branches en block with the broad ligament.

The donor ureter, distal to its crossing the internal iliac artery (distal 2-3 cm) is included in the uterine graft.

Anastomoses are performed with the robust internal iliac vessels.

Both living and deceased donor uteri are recovered with the (utero)ovarian vessels. The (utero)ovarian vein is used to supplement the venous drainage of the graft if needed. The (utero)ovarian artery has been rarely used. In the living donor, the ovaries have to be carefully preserved.

Besides the technique, there are other major differences between living and deceased donor uterine transplantation.

The supreme advantage of living donation is control of the timing of the operation and the ability to prepare both the donor and recipient for the transplant. This includes possible hormonal preparation of an older donor.

Greatest disadvantage is the risk to the donor. The risk is not exactly known but is expected to be low. Main concerns are the length of the donor operation and the extensive dissection of the pelvic vital structures of the donor, particularly the ureters, as already mentioned.

Supreme disadvantage of the deceased donor UTx is the shortage of female donors of reproductive age. The timing of the transplant cannot be controlled. Supreme advantage is the lack of risk to the donor.

In general, living donors have better long-term patient and graft survival outcomes. This is hardly an ad-

vantage in UTx. Contrary to other transplants, the uterine graft is the only known ephemeral graft. It is intended to be removed after the birth of one or two healthy babies.

Simultaneous with our work in the animal lab, we presented our efforts to the Ethics Board of the University of Miami. In collaboration with the Director of the Institute of Bioethics and Health Policy at the University of Miami, Dr Ken Goodman, we held a "Town Hall" meeting. Faculty and students of the University of Miami as well as interested members of the community and clergy were invited and we participated in lively discussions regarding the propriety of attempting Uterus Transplantations in humans.

Main concerns were related to the unknown risk of performing a non-vital transplant for a healthy person, the risk to the fetus and in case of living donation to the donor.

A mitigating factor was that the healthy recipient is not subjected to lifelong immunosuppression. The immunosuppression is stopped when the graft is removed and not given for life.

The outcome of the "Town Hall" meeting was positive overall, although, as expected the scrutiny was intense.

In the meantime, the Swedish team was ready to proceed with a human trial and invited me to participate. We performed 9 uterine transplants from living donors [2]. It was exactly at that time that I relocated from the University of Miami to the Cleveland Clinic.

It was also the beginning of a very close collaboration with the Department of Gynecology and Obstetrics at the Cleveland Clinic, one of the best in the World headed by Dr Tommaso Falcone.

I participated in all the Swedish cases, Dr Falcone joined me and with his teammate, Dr Rebecca Flyckt became enthusiastic partners.

Dr Falcone and I were impressed that even in the very experienced hands of the Swedish team, the donor operation took 8-10 hours including the very extensive dissection of vital structures, particularly the donor ureters.

For these reasons, at the Cleveland Clinic we decided to continue our focus in deceased donor transplants. The very elaborate process of Review by the Institutional review board had to be repeated. We obtained approval after 2 years of deliberations.

After several practice runs, we developed a simple method to perform the deceased donor hysterectomy safely [9]. It starts with a new "arrow shaped" incision which facilitates the pelvic dissection and expedites the organ recovery. It can be accomplished in 1.5 hrs (Figure 3, 4).

The first live birth from a live uterus donor was done in 2014 in Sweden [2]. It was followed in the same year by the first Uterus transplant in the US by a deceased donor which took place at the Cleveland Clinic [11]. Unfortunately, the graft failed because of an arterial anastomotic disruption of the left arterial anastomosis (Uterine to external iliac artery), due to candida endarteritis. This was a life- threatening complication. Thankfully, the patient recovered completely, but this serious complication necessitated an extensive, time-consuming review of the protocols as well as ethical review.

There has been some confusion about the "firsts"…

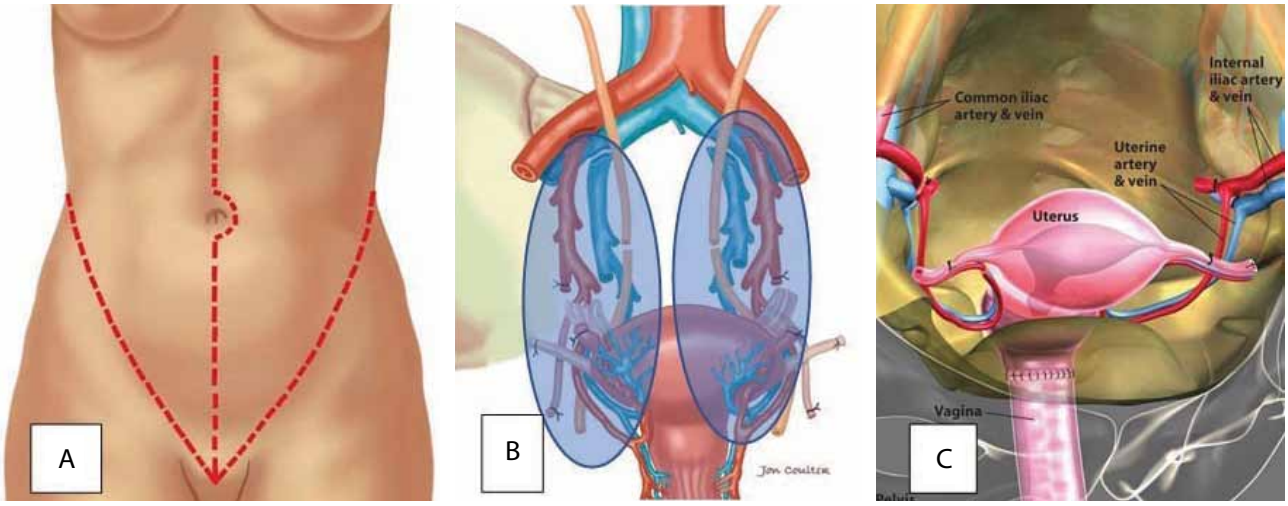

Figure 3. The deceased donor. Human UTx: A: Donor Incision, B: Vascular pedicles, C: Uterus in place.

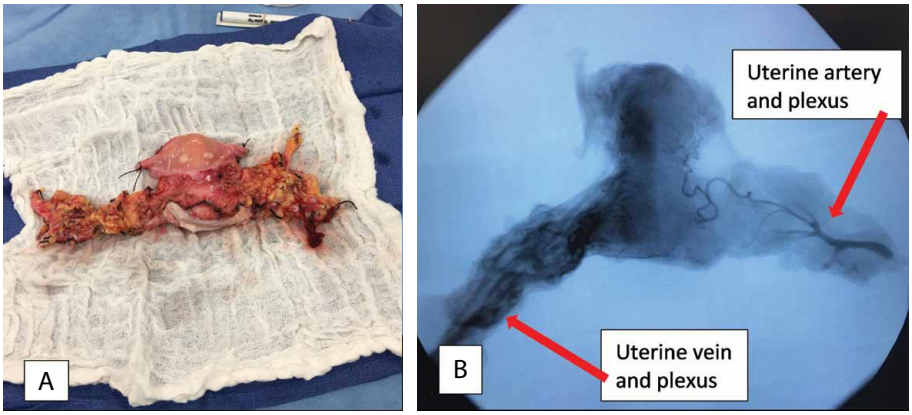

Figure 4 A: Uterine graft from deceased donor, 4b: ex vivo angiogram.

The definition of a successful uterine transplant is one that results in the birth of a healthy offspring.

The Turkish case [1], although technically successful was not recognized as "successful" till 2020 when the recipient delivered a healthy baby after multiple, heroic and protracted attempts.

In the meantime, the pioneering Swedish trial [2], in addition to the technical success, produced the first live birth followed by a series of more healthy babies. It proved, in a fairly short time, both the feasibility and efficacy of this operation.

The success of the Swedish trial was undoubtedly the most influential factor in the development of Uterine Transplantation worldwide. It encouraged new investigators to proceed using living donors, for the most part. It showed that UTx, although not vital, can nurture life and deliver it safely into this world.

The first live birth from a deceased donor took place in Brazil in 2017 [10]. It was followed by the first delivery of a healthy child from a deceased donor in the US at the Cleveland Clinic in a few months [12]. They were both momentous events showing that UTx from a deceased donor may be just as effective as the living donors.

Unfortunately, our reservations about living donation have been substantiated in the initial world experience. Every busy living donor program has seen at least one ureteral complication which required a surgical or endoscopic correction. No doubt, more experience will help optimize the techniques and further improve the results.

In the meantime, more successful UTxs with deceased donors, including the ones in Cleveland, have been reported invigorating the interest in deceased donors.

We have since performed additional 7 cases with one failure. There have been 4 healthy babies from our patients, the largest series to this day. We are in the process of in vitro fertilization for the remaining 2 (Figure 5, 6).

An International Registry of UTx is in the making. In the meantime, reports on worldwide experience are based on presentations at National and International Meetings.

It is estimated that there have been 60 UTxs performed worldwide with technical success in 90% of them. There have been more than 30 babies, all healthy. More babies are forthcoming as efforts for successful pregnancies continue in the technically successful cases.

Thus far, all uterine transplants have been financed by Institutional Grants and Private donations with the exception of one UTx from a living donor which has been "self-financed". Wide acceptance will result in more extramural funding which will help the dissemination of the procedure.

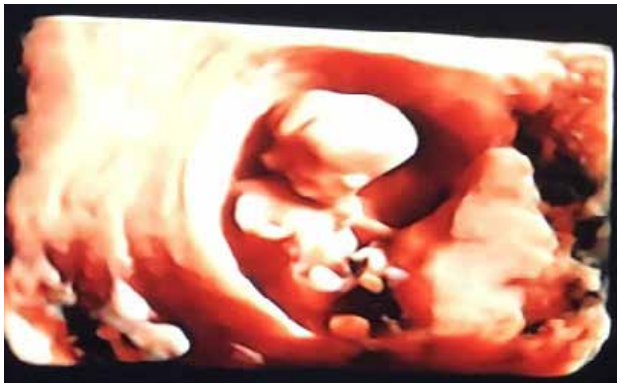

Figure 5. Doppler Ultrasound of the fetus midterm from our First Successful UTx.

Figure 6: The birth of the first baby in the US from a deceased donor: a magical moment.

The journey to UTx continues, but is no longer in uncharted waters. We landed in new territory, one that seems to be more fertile with each passing day.

Conflict of interest disclosure: *None to declare*

Declaration of funding sources: *None to declare*

Author contribution: *Andreas G Tzakis: conception, writing, data interpretation and review of the final draft of the article.*

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Viral dynamics of the Omicron variant in COVID-19 disease

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INTRODUCTION

The continued evolution of SARS-CoV-2, including the rapid accumulation of viral mutations to such an extent that new viral variants with different characteristics are emerging, has led to great concern about the ability of these variants to evade the immune response triggered by natural infections and/or vaccination. A large recent wave of infections has been caused by a new variant classified as B.1.1.529/Omicron. It was first reported by the Network for Genomics Surveillance in South Africa to WHO and classified as a SARS-CoV-2 variant of concern (VOC) on November 26, 2021 [1]. The Omicron variant has four sublineages B.1.1.529 (BA.1), B.1.1.529.1 (BA.1.1), B.1.1.529.2 (BA.2) and B.1.1.529.3 (BA.3), which differ in the number of mutations in the spike protein, with BA.1 having the highest number of mutations and currently being the dominant lineage [2] (Table 1).

The evolutionary history of Omicron is currently unknown because it is very different from the other SARS-CoV-2 variants and may have previously split from other variants, probably Alpha and Delta. Phylogenetic studies suggest that the emergence of Omicron may be related to immunocompromised individuals (e.g., HIV patients co-infected with SARS-CoV-2) harboring Omicron over a period of time, or it may be a host-spawning effect involving an evolutionary pathway in non-human species [3, 4]. The rapid international spread of the Omicron variant and its higher number of mutations compared to other variants, as well as the fact that some Omicron mutations are associated with escape from vaccine-induced immunity, pose a new challenge in the control and prevention of the COVID-19 pandemic [5].

Important questions have been raised about the impact of Omicron on transmissibility, disease severity, the effectiveness of existing COVID-19 vaccines in preventing severe disease, humoral response, and the role of T-cell immunity in vaccinated individuals.

The genetic profile of the Omicron variant and its impact on SARS-CoV-2 characteristics

The Omicron variant has the highest number of mutation sites compared with other SARS-CoV-2 variants, half of which were identified in the spike glycoprotein (S). In total, more than 60 substitutions, deletions, and insertions were reported in the Omicron variant. In the open reading frame genes (ORF) encoding the nonstructural proteins of SARS-CoV-2, the Omicron variant has 9 amino acid substitutions and 3 amino acid deletions. It has been speculated that the deletion of 3 amino acids in ORF1a at sites L3674, S3675, and G3676 may prevent the ability of infected cells to degrade viral components, which would contribute to evasion of the innate immune system [6].

Substitutions and deletions were also dicovered in the structural proteins of SARS-CoV-2, including the envelope, membrane, and nucleocapsid (N) proteins [7]. Two mutations in the N protein, R203K and G204R, have been associated with increased subgenomic RNA expression and viral load [8, 9].

At least 30 amino acid substitutions, 3 small deletions

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Key words: *SARS-CoV-2; Omicron variant; COVID-19*

Table 1. *SARS-CoV-2 variants of concern (VOC) as designated by WHO.*

WHO label	Country of 1st detection	Earliest documented samples	Pango lineage
Apha (α)	UK	Sept. 2020	B.1.1.7
Beta (β)	S. Africa	May 2020	B.1.351
Gamma (γ)	Brazil	Nov. 2020	P.1
Delta (δ)	India	Oct. 2020	B.1.617.2
Omicron (ο)	Botswana, S. Africa, multiple countries	Nov. 2021	B.1.1.529, B.1.1.529.1 B.1.1.529.2 B.1.1.529.3

and 1 short insertion of 3 amino acids were identified in the S protein, of which 15 mutations are located in the S1 receptor binding domain (RBD) of the S protein. Mutation D614G in the S protein, common to all SARS-CoV-2 variants, has been associated with higher viral load in the upper respiratory tract [10, 11]. Increased binding between spike and angiotensin-converting enzyme 2 (ACE2) may be due to the N501Y mutation in the S protein, which is present in the Omicron, Alpha, Beta, and Gamma variants and, in combination with the H69/V70 deletion, leads to higher transmissibility [12, 13].

Computer modeling has confirmed that the Omicron variant mutations cause tighter binding at the ACE2-RBD interface, strengthening hydrogen bonds and increasing the accessible surface area [14]. The Omicron variant mutations have also been associated with an increased electrostatic potential of the S protein at the RBD interface with ACE2 compared to the Delta variant, which could lead to a stronger S-ACE2 interaction affinity since ACE2 has a negative electrostatic surface potential. Considering that the entry of SARS-Cov-2 into host cells depends on the binding of RBD to ACE2, the tighter binding of RBD to ACE2 and the stronger RBD-ACE2 interaction affinity caused by the mutations of the Omicron variant might increase the infectivity of SARS-Cov-2 in the upper airway epithelium. The interaction of the S protein with other macromolecules, such as antibodies, could also be affected by the altered electrostatic surface potential of Omicron RBD [15]. By mutating N679K and P681H near the furin cleavage site, Omicron could promote enhanced fusion and infectivity. The amino acid substitutions near the furin cleavage site could insert amino acids that facilitate cleavage of the spike into S1 and S2 and promote fusion between the virus and the host cell membrane [7]. Examination of the changes in the RBD mutations of Omicron in the binding free energy (BFE) of the S-ACE2 protein complex revealed a 10-fold increase in the contagion capacity of Omicron compared to the original SARS-CoV-2 strain and a 2-fold increase in the contagion capacity of Omicron compared to the Delta variant, mainly due to the RBD mutations N440K, T478K, and N501Y [16] (Figure 1).

The ability of the Omicron variant to escape immunity

Omicron has accumulated a higher number of mutations in RBD compared to Delta [7]. Considering that RBD is the main target for neutralizing antibodies, great concern has been expressed about the ability of Omicron to escape immune recognition and whether existing antibody treatments and vaccines could still be effective.

A clue to the possible resistance of Omicron to neutralization by antibodies was provided by structural analysis studies, which indicated that certain mutations (G446S, Q493R, and G496S) at the S-RBD could create steric interference for antibody binding to the RBD, while other mutations (E484A and Y505H) could abolish interaction affinity with antibodies [17]. The RBD mutations K417N, E484A, and Y505H were held responsible for the high potential of Omicron to interfere with the binding of about 185 antibodies with the S protein [16].

As for monoclonal antibody (mAb) treatment, Omicron's RBD mutations are thought to interfere with the efficacy of Eli Lilly's mAb cocktail (against K417N, E484A, Q493R), Celltrion's regdanvimab antibody (against E484A, Q493R, and Q498R), and the Rockefeller University mAbs (against E484A), whereas the impairment of the efficacy of Regeneron's mAb cocktail is thought to be low [16].

Some studies have also examined the resistance of Omicron to neutralization by antibodies. In 3 longitudinal cohorts, 169 plasma samples were collected from convalescent individuals who had received or not

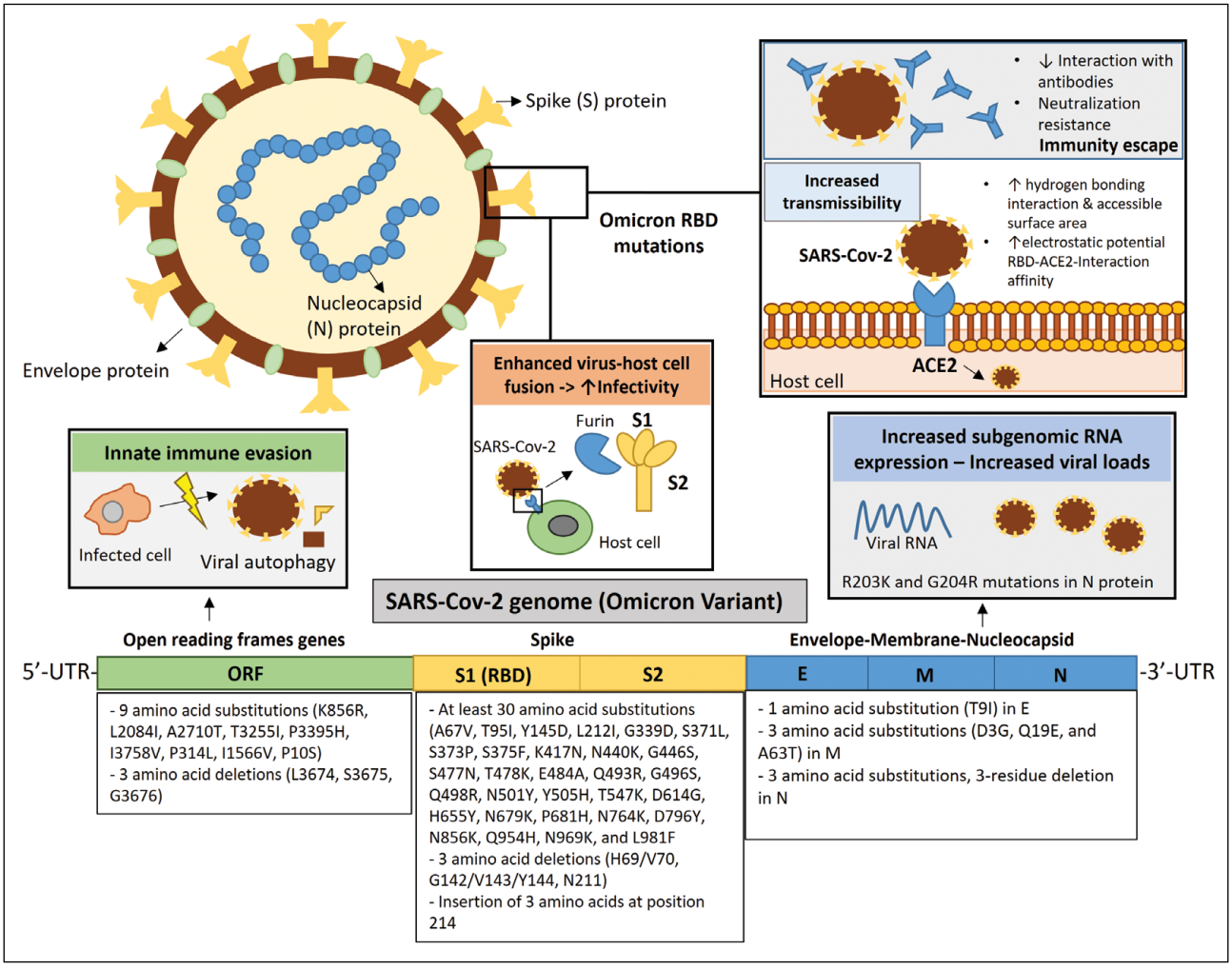

Figure 1. The genetic profile of the Omicron variant and its implications for the viral properties of SARS-CoV-2. The Omicron variant has more than 60 substitutions, deletions, and insertions located in open reading frame genes (ORF), spike glucoprotein (S), envelope protein (E), membrane protein (M), and nucleocapsid (N) protein. Deletion of 3 amino acids in ORF1a at sites L3674, S3675, and G3676 is thought to prevent the ability of infected cells to degrade viral components, contributing to evasion of the innate immune. Two mutations in N protein, R203K and G204R, have been associated with increased subgenomic RNA expression and viral load. Enhanced binding between spike and angiotensin-converting enzyme 2 (ACE2), leading to higher transmissibility was attributed to Omicron mutations in the S1 receptor-binding domain (RBD). According to computer modeling, the Omicron variant mutations could increase the hydrogen bonding interaction and increase the buried surface area accessible to the solvent. Omicron variant mutations were also associated with an increased electrostatic potential of the S protein at the RBD interface with ACE2, which could lead to a stronger interaction affinity of S-ACE2. The interaction of the S protein with antibodies could also be affected by the altered electrostatic potential of the Omicron RBD surface. Structural and clinical studies have shown that Omicron exhibits strong resistance to neutralization by antibodies, indicating the risk of immune escape. Increased infectivity may be favored by Omicron because it has mutations near the furin cleavage site that facilitate cleavage of the spike into S1 and S2, promoting virus-host cell membrane fusion.

received 2 doses of Pfizer/BNT or Moderna mRNA vaccine, from uninfected individuals who had received 3 doses of Pfizer/BNT mRNA vaccine, and from uninfected individuals who had received J&J Ad26 vaccine at approximately 1, 5-6, and 12 months after initial vaccination or infection. Neutralizing antibody titers were measured in plasma samples with pseudotyped virus containing the original Wuhan-hu-1 strain or the Omicron variant or a laboratory-developed neutralization-resistant SARS-CoV-2 spike (PMS20). In plasma from convalescent, 2-dose vaccinated and nonvaccinated individuals, neutralization activity was reduced 30- to 60-fold against PMS20 and Omicron compared to the original strain, and the reduced neutralization was even more pronounced

in plasma from recipients of 2 mRNA vaccine doses (30- to 180- fold less effective compared with Wuhan-hu-1). In contrast, administration of additional mRNA vaccine doses to infected individuals or those vaccinated with 2 mRNA doses resulted in a 38- to 154-fold and 35- to 214-fold increase in neutralizing activity against Omicron and PMS20, respectively [18].

Decreased neutralizing ability of other recent vaccines against Omicron, including the inactivated virus vaccine BBIBP-CorV and the recombinant dimeric RBD vaccine ZF2001, has also been reported [19]: Neutralization tests were performed using plasma from 37 participants divided into 4 groups: (1) 7 participants after 3-4 months of past SARS-CoV-2 breakthrough infection caused by the Delta variant who had been immunized with 2 doses of the inactivated Sinovac-CoronaVac vaccine before infection, (2) 10 participants who had been immunized with 2 doses of BBIBP-CorV, (3) 10 participants who received a third homologous booster dose of BBIBP-CorV, and (4) 10 participants who received a third heterologous booster dose of BBIBP-CorV/ ZF2001. A plasma pseudovirus neutralization test (pVNT) was performed that included pseudotyped viruses with prototype virus, Beta, Delta, and Omicron variants. Fourteen days after administration of 2 doses of inactivated vaccines, the pVNT titer was lowest for the Omicron variant in 80% of the samples. However, after booster vaccination, positive neutralization sensitivity for the Omicron variant was observed in 100% of the samples.

Although Omicron may have the ability to evade humoral immunity, there are encouraging data on the effect of Omicron on T-cell immunity. Redd et al [20] investigated whether epitopes of the Omicron variant recognized by CD8+ T cells were significantly mutated in recovered COVID-19 patients. The identification of only 1 mutation (T95I) in the spike protein that overlapped with a CD8+ T-cell epitope (GVYFASTEK) associated with two HLA alleles (HLA*A03:01 and HLA*A11:01), and the demonstration of T-cell reactivity in individuals carrying this modified epitope suggests that previously induced anti-SARS-CoV-2 CD8+ T-cell responses may still be active against Omicron and that extensive T-cell escape mutations have not yet developed in SARS-CoV-2.

In addition, a recent analysis of clinical and epidemiologic data from 69,279 SARS-CoV-2-positive patients, 52,297 with S gene drop out (SGTF, presumably the Omicron variant) and 16,982 without SGTF (presumably the Delta variant), found that SARS-CoV-2 infections with the Omicron variant were associated with a substantially lower risk of severe clinical endpoints and shorter length of hospital stay. (Lewnard et al., Pre-print. MedRxiv. 2022. https://doi.org/10.1101/2022.01.11.22269045). However, we do not yet know how infection with all Omicron sublineages affects disease progression.

Overall, Omicron may be better able to evade immune recognition compared with the original SARS-CoV-2 strain and other variants. Although booster vaccination may show promise in restoring the observed reduced neutralizing capacity against Omicron, evaluation of the impact of the third (or fourth) booster vaccination on vaccine efficacy is ongoing because very few studies have been published to date that have examined the neutralizing capacity of various homologous and heterologous booster vaccines against Omicron. It appears that Omicron will not be the last variant, so the development of monovalent vaccines may no longer be the solution. Understanding the specific virology and biology of each new variant is essential to monitor the dynamics of genetic changes and translate this knowledge into more effective prevention strategies for the COVID-19 pandemic.

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ORIGINAL RESEARCH ARTICLE ACHAIKI IATRIKI | 2022; 41(1):18–24

Management of a COVID-19 cluster of cases in a closed nursing healthcare facility after the start of the vaccination program – The role of COVID-19 vaccination

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Abstract

Background: COVID-19 disease has been occupying the scientific community for 20 months with a wealth of data emerging daily on the effectiveness and safety of the various interventions proposed. Vaccination probably represents the most promising intervention.

Methods: A retrospective study was conducted in 45 patients and 59 staff members of a rehabilitation center during an epidemic outbreak. Data from the center's medical records were used to determine vaccination status, positivity for COVID-19 and disease characteristics. Furthermore, the presence of a statistically significant relationship between vaccination status and incidence of the disease as well as of disease characteristics including viral load was examined. The statistical package SPSS v24 was used for the descriptive and statistical analysis.

Results: The mean values of CRP, WBC and lymphocytes at diagnosis were 1.9 mg/dl, 6425/μl and 1303/μl, respectively. Age was statistically significantly related to the severity of the disease. High viral load (CT- cycle threshold <25) was associated with about a 50-time higher death risk ($p<0.05$). A person fully vaccinated is 19 times more likely not to be infected ($p<0.001$, vaccination effectiveness of 95%). Furthermore, a negative correlation between vaccination and the presence of infection symptoms ($p=0.035$) was observed.

Conclusion: Complete vaccination is more likely to protect against the possibility of infection or severe disease. It is important, however, to complete the second dose of the vaccine. On the other hand, measuring antibodies following vaccination does not seem to guarantee immunity and may predispose to dangerous behavior.

Key words: *Vaccine; COVID; viral load; CT (cycle threshold)*

INTRODUCTION

COVID-19 has been proved a major threat to public health provoking worldwide political and economic reactions and is now recognized as one of the 10 largest pandemics in history. It is currently 6th in deaths (0.07% of the population) and the small percentage is related to the large increase in population in recent decades [1]. Currently, more than 254 million cases have been described with 5 million deaths.

This is a new disease that is being monitored very closely and all information must be published as scientifically as possible so that conclusions can be drawn

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quickly and clearly. Information disclosure (not misinformation) may change the course of this pandemic. More than 200,000 papers have been published since 2020 regarding COVID-19 and more than 17,000 regarding COVID-19 vaccination according to Scopus and PubMed databases.

Various therapeutic interventions have emerged [2,3], but the most promising so far seems to be primary prevention through vaccination of the population [4]. Vaccination is now widespread in Greece, starting from the beginning of 2021. However, there was a lot of skepticism against vaccines, even among medical staff [5,6].

The purpose of this study was to investigate the outbreak of COVID-19 cases in a rehabilitation center and to examine evidence on the preventive effect of vaccination. Furthermore, associations between viral load and severity of the disease were assessed.

METHODS

This is a retrospective study regarding a cluster of cases between March 16 and 30 April 2021. The study population consists of 45 patients and 59 medical, paramedical and other staff of a rehabilitation center in an area with an epidemic outbreak. In this context, the measures taken before the first case are reported and compared to the measures taken after the outbreak of cases. Vaccination status was defined by the relevant certificate, while testing for COVID-19 was based either on rapid Ag tests or PCR test, with all positive Ag tests being confirmed by PCR. Biochemical and clinical parameters of infected individuals were collected from the center's medical files. Viral load was determined by cycle threshold (CT) in the PCR. We examined all associations between vaccination and the incidence of COVID-19, as well as the outcome and course of the disease. Furthermore, correlation between viral load and disease outcome was examined. The statistical package SPSS v24 was used for the descriptive and statistical analysis.

RESULTS

The study population included a total of 104 people, 45 hospitalized patients (55.6% women, mean age 73.3 years) and 59 staff personnel or attendants (69.5% women, mean age 39.8 years). Participants' characteristics are shown in Table 1.

A total of 23 people were infected with the SARS-CoV-2 (17 patients, 5 staff members and 1 attendant), 7 men (30.4%) and 16 women (69.6%). The mean age of infected individuals was 65 years and that of uninfected individuals was 51.2 years. The descriptive characteristics of the infected group are shown in Table 2, while the original immunity status of the study group can be seen in figure 1.

Within the infected group, 3 (13%) were fully vaccinated (2 staff members and one patient). However, one patient had just been vaccinated with the second dose at the time of diagnosis, so he should be considered as incompletely vaccinated.

Among the fully vaccinated patients, only 3 (4.9%) tested positive and were all asymptomatic, despite daily exposure to the virus (Table 3). One of them had just been vaccinated with the second dose, in the second patient no antibodies were measured and the third had antibodies more than 150 times above the laboratory limit.

Table 1. *Demographics of the study group.*

Group	Men		Women		Total	
	No	Mean Age (SD)	No	Mean Age (SD)	No	Mean Age (SD)
Patients	20	68.2 (17.1)	25	77.4 (13.2)	45	73.3 (15.6)
Nursing personnel	13	35.8 (5.1)	22	36.3 (9.9)	35	36.1 (8.4)
Medical personnel	2	47.5 (7.7)	3	39.3 (19)	5	42.6 (14.7)
Kitchen personnel	1	43	5	46.6 (10.6)	6	46 (9.6)
Cleaning personnel	0	0.0	4	50.8 (6.5)	4	50.8 (6.5)
Reception	1	33	4	37.5 (7.8)	5	36.6 (7.1)
Relatives/ caregivers	1	28	3	60 (5)	4	52 (16.5)
TOTAL	38	53.4 (20.5)	66	54.8 (21.7)	104	54.3 (21.2)

Table 2. *Descriptive characteristics of the infected and non-infected individuals.*

	Men		Women		Total	
	No	Mean Age (SD)	No	Mean Age (SD)	No	Mean Age (SD)
Infection	7	54.6 (16.7)	16	69.6 (19.6)	23	65 (19.7)
No Infection	31	53.1 (21.5)	50	50.1 (20.3)	81	51.2 (20.7)

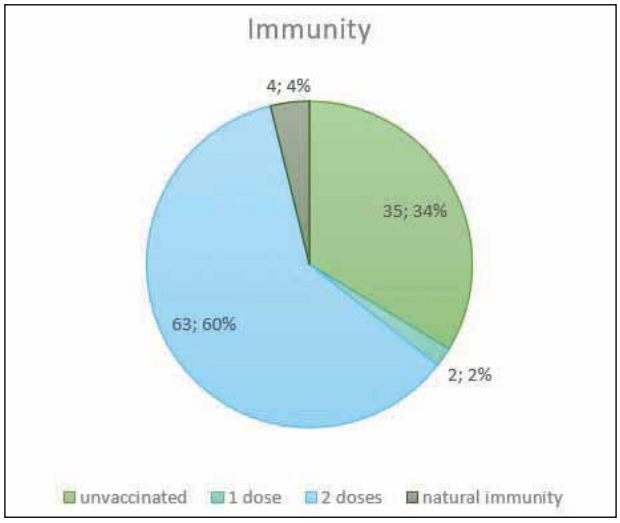

Figure 1. Immunity characteristics of the study population (number of persons, percentage).

The total number of cases developed in 3 phases: In the first phase, there was no case isolation (incidents were referred to the hospital for admission) and their relatives could visit them - albeit for a limited time – applying all individual protection measures and hand washing. In the second phase, case-limiting measures were developed with periodic patient and staff testing. In the third phase, many new incident cases were discovered among new admissions from surrounding hospitals, and thus they remained in isolation for 5 days.

At the beginning of the study period, 5 patients and 1 attendant were found positive. The subsequent follow-up examinations revealed 4 additional patients and 2 staff members. All 12 were unvaccinated. Afterwards, when the measures were fully implemented, 11 more people were found positive, all of them unvaccinated. Testing during admissions yielded 4 positive results. Another 4 patients (all unvaccinated) and 2 nurses (one vaccinated) were found to be positive later on. Furthermore, the doctor of the special isolation wing was tested positive for SARS-CoV-2, although he was fully vaccinated and developed antibodies after his second dose and two weeks before the cluster of cases. After the full implementation of the measures (protection measures, frequent sampling, ban on visits, completion of vaccination of patients and staff), the last positive case appeared 20 days after the first case and the operation of the special ward was suspended 45 days later (from 16 March to 30 April 2021).

In terms of incident tracking, the initial cases were attributed to the hospital of origin or attendants, since the overall control of the staff was negative. Two cases were of unknown origin (frequent contact with each other - one of the two is considered the first case), 8 cases (34.7%) were considered to be of hospital origin or by a companion, 9 individuals (37.1%) were infected by another patient (close contacts) and 4 people (17.4%)

Table 3. *Vaccination status in infected and uninfected persons.*

			Full vaccination		Total
			No	Yes	
Infection	Yes	People	20	3	23
		% of infected	87.0%	13.0%	100.0%
		% of total	19.2%	2.9%	22.1%
	No	People	19	62	81
		% of infected	23.5%	76.5%	100.0%
		% of total	18.3%	59.6%	77.9%

were estimated to have been infected by staff found positive.

Regarding infected individuals' outcome, from the 23 people, 9 (39.1%) had to be transferred to the hospital, 5 of whom finally died (21.7%). Recovery without the need for hospital admission was achieved in 14 people (60.9%), and 4 people (17.4%) recovered after hospitalization (Figure 2). Age was statistically significantly related ($p < 0.05$) to the severity of the disease (Figure 3).

All patients were administered the same therapeutic regimen with dexamethasone and azithromycin (or respiratory quinolone) on symptoms and only the need to administer oxygen with a venturi mask > 35% was an indication for hospital referral, given the heavy load on the health system at that time.

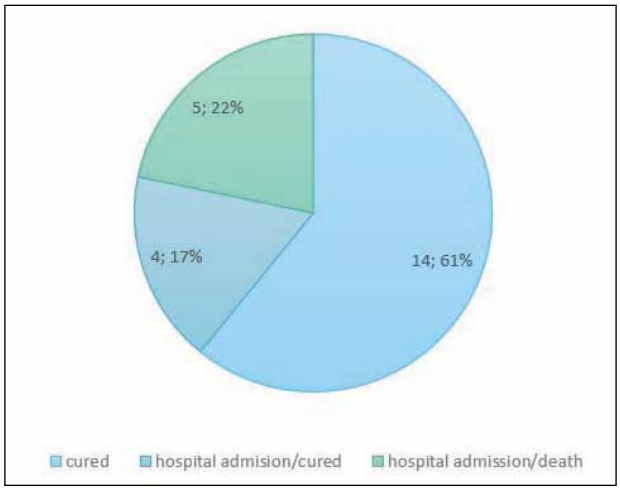

Figure 2. Disease outcome in infected persons (number of persons, percentage).

43.5% (10 people) of positive cases were asymptomatic, half of which had received at least 1 dose of the vaccine. More specifically, 3 were fully vaccinated and 2 had received 1 dose of vaccine. Of the 13 who showed symptoms, 92.3% had not been vaccinated and 1 person had received 1 dose of vaccine. Sixteen patients were diagnosed asymptomatic and 5 of them (31.2%) showed symptoms such as fever or desaturation on the 9th day.

The mean values of CRP, white blood cells and lymphocytes at diagnosis were 1.9 mg/dl, 6425/μl and 1303/μl respectively. Considering all the parameters that showed a statistically significant correlation with the COVID-19 infection, it appears that full vaccination significantly protects against the possibility of infection. A person who is fully vaccinated is 19 times more likely not to be infected than someone who is not vaccinated (b coefficient = 19,478, 95% CI 5,114 to 74,186, $p < 0.001$). Although the sample is small, there is also evidence of a negative correlation of vaccination with the presence of infection symptoms (spearman rho = -0.441, $p = 0.035$).

The maximum viral load, as estimated from the detection cycles in PCR (cycle threshold-CT), seems to show a statistically significant correlation with the probability of death ($p < 0.05$), although the sample is quite small. In fact, considering gender and age, it seems that having a high viral load (CT <25) is associated with

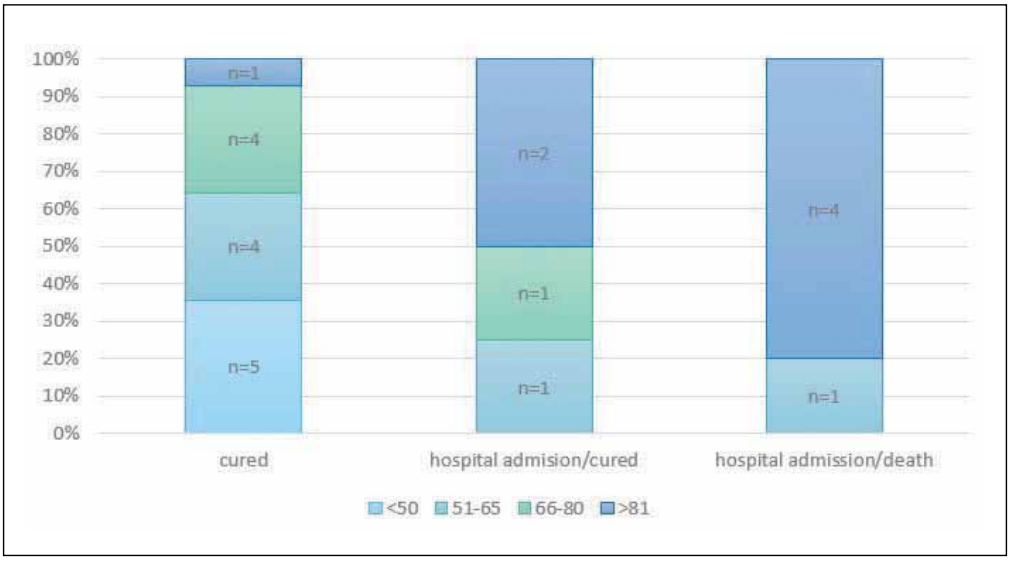

Figure 3. Age and the disease outcome.

an approximately 50-time higher risk of death than the lowest viral load (b coefficient = 48,728, 95% CI 1,061 to 2238,403, $p < 0.05$).

DISCUSSION

At a time of increasing demands from health systems, it is necessary to draw conclusions from the plethora of incidents managed by health facilities at a local level, from both the public and private sector. Since there is much confusion about the quality and type of information provided to the public and health professionals, it is important to disseminate scientifically valid information to the medical community and the public [7–9].

In the present study we were not able to draw clear conclusions about therapeutic interventions, but significant findings emerged regarding vaccination effectiveness. Research has so far shown that vaccination effectiveness increases with booster vaccination, achieving levels of effectiveness that exceed 90% [10–13]. Protection levels decline several months after vaccination, leading to the possibility of future booster shots. Table 4 presents some of these studies. Vaccination is even more effective regarding symptomatic disease. This study has found similar levels of efficacy, reaching 95% for documented disease and 100% for serious disease needing hospitalization, even though the sample size was rather small. However, an environment of mass exposure to the virus is not easy to find, so this study contributes to the evaluation of vaccine efficacy.

In a closed community such as a rehabilitation center, where there is significant and close contact between medical, nursing staff and patients, the spread of a highly infectious virus would quickly lead to a lockdown of the facility [14]. However, nobody among the vaccinated

Table 4. *Effectiveness of mRNA vaccines according to several studies.*

Effectiveness regarding documented infection				
	Effectiveness 14 days after first dose	Effectiveness 14 days after second dose	Effectiveness 42 days after second dose	Effectiveness >69 days after second dose
Bianchi, Francesco Paolo, et al. Vaccines (2021) [10]	97.7%	94.8%	83%	81%
Angel, Yoel, et al. *JAMA* (2021) [12]		81%		
Dagan, Noa, et al. *New England Journal of Medicine* (2021) [13]	46%	92%		
Polack, Fernando P., et al. *New England Journal of Medicine* (2020) [11]	52.4%	94.8%		
Present study		95.4%		
Effectiveness regarding symptomatic infection				
	Effectiveness 14 days after first dose	Effectiveness 14 days after second dose	Effectiveness 42 days after second dose	Effectiveness >69 days after second dose
Bianchi, Francesco Paolo, et al. Vaccines (2021)[10]	99.2%	97.2%	85%	88%
Angel, Yoel, et al. *JAMA* (2021) [12]		97%		
Dagan, Noa, et al. *New England Journal of Medicine* (2021) [13]	57%	94%		
Present study		100%		

persons (patient or staff) appeared to have the disease, and the few who were infected were asymptomatic. All the measures required by the literature and local legislation [15] (personal protection measures, frequent sampling, suspension of visitation, completion of vaccination of patients and staff) played an important role in case control.

A separate explanation could be given for the 3 cases of vaccinated individuals who were found positive. In the first case, the diagnosis was made 1 day after the second dose, therefore it was possible that no antibodies had developed, given the patient's age. In the second case, although no antibodies were measured, the presence of diabetes mellitus could lead to a reduced immune response, which has been reported in the existing literature [16]. The World Health Organization had proposed another type of vaccine than mRNA in patients with diabetes due to a lack of efficacy data in these populations initially [17]. In the 3rd case, that of a doctor, increased exposure to the virus due to the daily examination of patients (the same doctor was in charge of taking the samples in the emergency room) as well as the fact that, due to the increased demands and needs of the patients, he had to change protective equipment several times during the day in order to examine patients. These procedures reasonably increase the likelihood of error, despite adequate training and knowledge. Studies have shown that the nursing staff became infected in 80% of cases when the uniform was removed [18]. At this point, the illusion of the protection of the vaccine should be emphasized, since the development of a high titer of antibodies could lead to a lack of vigilance.

The use of cycle thresholds in PCR was not associated with the duration of positivity but seems to be related to the severity of the disease, as other studies have shown in the past [19], making it a useful tool, especially in the elderly.

In conclusion, the most important result of the study is that the application of complete vaccination significantly protects against the possibility of infection or severe disease. Vaccinated people were found to be about 20 times less likely to become infected while none were significantly ill in the study population. It is important, however, to emphasize that full protection is achieved 10 days after the 2nd vaccine dose. On the other hand, measuring antibodies following vaccination does not appear to guarantee immunity and may predispose to careless or even dangerous behavior.

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Prevention of colorectal cancer and the importance of primary care

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Abstract

Colorectal cancer (CRC) is one of the most frequent and deadliest types of cancer. Its incidence seems to be increasing in age groups 20-49 years old, without a parallel increase in mortality. Improvement of nutrition with the inclusion of more fruit and vegetables and less consumption of red meat, along with more frequent exercise are the most important elements of primary CRC prevention. Screening is arguably a valuable tool for CRC prevention. Current European guidelines recommend starting screening for CRC in the general population at the age of 50, while the American Cancer Society recommend screening start at the age of 45. Colonoscopy is considered the most reliable screening test for the detection of CRC, but at the same time it is the most inconvenient to conduct both for patients and doctors. After performing any test other than colonoscopy, any abnormal findings should be followed up with colonoscopy. The role of primary care physicians in the prevention of CRC is very important, so there should be constant updates on behalf of physicians and the general population on current CRC prevention guidelines and available screening tests.

Key words: *Colorectal cancer; prevention; screening; primary care*

INTRODUCTION

Colorectal cancer (CRC) is a common and lethal disease. The risk of developing CRC is influenced by both environmental and genetic factors. CRC incidence and mortality rates vary significantly around the world. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females. Death rates from CRC have declined progressively since the mid-1980s in the United States and in many other western countries. This improvement in outcome can be attributed, at least in part, to detection and removal of colonic polyps, detection of CRCs at an earlier stage, and more effective surgical and adjuvant treatments. Current efforts to reduce CRC incidence and mortality in adults younger than 50 years old are focused on identifying those eligible for earlier age surveillance, based on family history, and promoting both clinician and patient awareness of symptoms that could potentially point to malignancy, such as persistent rectal bleeding at any age [1].

In this review, we provide an overview of the epidemiology and risk factors of CRC, the importance of preventive medicine, the screening tests and current guidelines for CRC prevention, along with factors influencing adherence to CRC screening programmes. Moreover, we focus on the important role of primary care in CRC prevention, and suggest some actions that could improve its function.

Epidemiology and pathophysiology of colorectal cancer

In the United States, both the incidence and mor-

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tality of CRC have been slowly but steadily decreasing. Annually, approximately 149,500 new cases of large bowel cancer are diagnosed, 104,270 of which are colon cancer, and the remainder are rectal cancer. Annually, approximately 52,980 Americans die of CRC, accounting for approximately 8 percent of all cancer deaths [1]. In the European Union (EU) in 2020, it was estimated that CRC accounted for 12.7% of all new cancer diagnoses and 12.4% of all deaths due to cancer. That made it the second most frequently occurring cancer (after breast cancer) and the second cause of cancer death (after lung cancer) [2]. According to GLOBOCAN 2020, 12.2% of all new cancer cases and 11.8% of all deaths due to cancer in Greece were attributed to CRC, making it the second most frequently occurring and second most lethal type of cancer in the country [3].

Age is a major risk factor for sporadic CRC. Large bowel cancer is uncommon before the age of 40; the incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter. More recent data from the United States Surveillance, Epidemiology, and End Results (SEER) database and other Western cancer registries suggest that CRC incidence is increasing in the under age 50 group while it is decreasing in older groups. In the United States, the incidence of CRC in males and females under the age of 50 steadily increased at a rate of 2 percent per year from 1995 through 2016 [1]. In Europe, a study by Fanny ER Vuik et al, published in Gut 2019, showed that during the period 1990-2016, the incidence of CRC increased in Europe among subjects between the ages of 20 and 49 years old, with the fastest rise in incidence occurring in the youngest age group (20-29 years old). The rise in incidence was more prominent for colon cancer than for rectal cancer, but it was not associated with a similar rise in mortality. They suggest that, while current guidelines in Europe recommend starting CRC screening from the age of 50, a continued increase in incidence in people aged under 50 will require to lower the age to start screening, similarly to the American Cancer Society (ACS) guideline of 2018 [4].

The vast majority of tumors of the colon and rectum are carcinomas. Other histologic types (neuroendocrine neoplasms, hamartomas, mesenchymal tumors, lymphomas) are relatively unusual. Among the carcinomas, more than 90 percent are adenocarcinomas [5]. The disease begins as a benign adenomatous polyp, which develops into an advanced adenoma with high-grade dysplasia and then progresses to an invasive cancer over a period of 10-20 years. There are many genes and growth factor pathways that drive the progression of CRC, some of them being activated (oncogenic mediators such as KRAS, BRAF, PTEN, EGFR) and others deactivated (tumor suppressor factors such as APC, b-Catenin, TP53) during the process [6].

Types of prevention and their importance

Preventive measures have decreased morbidity and mortality from both acute and chronic conditions [7]. There are three main types of prevention. Primary prevention refers to actions before health effects occur, through actions such as vaccinations, altering risky behavior (poor eating habits, tobacco use), and banning substances known to be associated with disease. Secondary prevention (screening) aims to identify diseases in the early stages, before the onset of signs and symptoms, through measures such as mammography and regular blood pressure testing. Tertiary prevention refers to managing disease post diagnosis to slow or stop disease progression through measures such as chemotherapy, rehabilitation, and screening for complications. Most prevention suggestions are primary or secondary prevention efforts for individuals [8]. Much of medical practice is based on a disease/treatment model rather than a prevention model in that the predominant focus is on treating existing symptoms and conditions. While few would argue this approach is necessary for acute conditions, there is some question as to whether this is the most efficient and effective way of delivering preventive care. A major task, therefore, is to modify the traditional medical model to incorporate more preventive services [7].

Risk factors and primary prevention of colorectal cancer

Several potentially modifiable factors, including obesity, diabetes, tobacco use, excess consumption of alcohol, excess consumption of processed meat, and lack of physical activity, have been consistently identified as risk factors for CRC in observational studies [1]. Primary prevention is based on altering modifiable risk factors. Several studies have shown that high intake of red and processed meats, highly refined grains and starches, and sugars are related to increased risk of colorectal cancer. Replacing these foods with poultry, fish, and plant sources as the primary source of protein; unsaturated fats as the primary source of fat; and unrefined grains,

legumes and fruits as the primary source of carbohydrates is likely to lower the risk of colorectal cancer. With respect to lifestyle, compelling evidence indicates that avoidance of smoking and heavy alcohol use, prevention of weight gain, and maintenance of a reasonable level of physical activity are associated with markedly lower risks of CRC [9]. Medications such as aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) are associated with substantial reductions in CRC risk, probably achieved through increased apoptosis and impairment of tumor cell growth by inhibition of cyclooxygenase-2, though their utility is affected by associated side effects, most frequent of whom are gastroduodenal toxicity and, with non-aspirin NSAIDs, increased cardiovascular risk [1,9,10]. Modifications in diet and lifestyle, alongside screening, are the major factors that can substantially reduce the risk of colorectal cancer [1,9].

Although the majority of CRC cases are sporadic, there are certain hereditary forms of CRC cancer, such as Familial Adenomatous Polyposis (FAP) and Lynch syndrome, that can be diagnosed and followed up with screening. Other factors that influence screening recommendations are age greater than 45 years old, a personal or family history of sporadic CRC (and possibly large or advanced adenomas), inflammatory bowel disease, and a history of abdominal radiation. Other risk factors have been identified, including African-American race, sex, acromegaly, and a history of renal transplantation, but their influence on screening recommendations has been variable [1].

Screening tests

Screening is the process of searching for cancer or pre-cancer abnormalities, such as colon adenomas, in people who have no symptoms of disease. Screening is the main form of secondary prevention of CRC**.** According to the ACS, there are two main types of screening tests for CRC: those based on analyzing feces samples and those based on visualization of the colon and rectum. The first category includes guaiac-based fecal occult blood test (g-FOBT), fecal immunochemical test (FIT) and stool DNA test. The second category includes flexible sigmoidoscopy, colonoscopy and computed tomography colonography (CT colonography) [11]. The methodology of performance of each test is analyzed below, and the advantages and disadvantages of each test are displayed on Table 1.

The g-FOBT identifies hemoglobin by turning guaiac reagent-impregnated paper blue as the result of a peroxidase reaction. Guaiac testing of stool samples can identify hemoglobin that may be present due to bleeding from a colon lesion or for other reasons [11,12]. The FIT also checks for non-visible blood in the stool from the intestine. The idea behind this type of test is that blood vessels in larger colorectal polyps or cancers are often fragile and easily damaged by the passage of stool. The damaged vessels usually bleed into the colon or rectum, but only rarely is there enough bleeding for blood to be seen by the naked eye in stool [11,12]. Multitarget stool DNA testing (MT-sDNA, also known as FIT-DNA, called Cologuard in the United States), is a composite of tests that include molecular assays to test for DNA (KRAS) mutations, a gene amplification technique to test for methylation biomarkers associated with colorectal neoplasia, and an immunochemical assay (FIT) to test for hemoglobin from blood that may be shed into the stool by colorectal lesions. DNA shed into stool by colorectal neoplasms may reveal genetic mutations and epigenetic changes occurring during carcinogenesis [11,12].

A flexible sigmoidoscopy is similar to a colonoscopy except it does not examine the entire colon. The 60 cm flexible fiberoptic sigmoidoscope reaches from the rectum up to the splenic flexure, allowing visualization of lesions, biopsies, and removal of polyps in the left-side of the colon only [11,12]. Colonoscopy is performed by a trained clinician using a flexible fiberoptic endoscope to directly visualize the interior of the rectum, colon, and a portion of the terminal ileum. It allows the visualization of lesions, biopsy and removal of polyps in the whole colon [11,12]. Finally, CT colonography involves obtaining multiple, thin-slice CT data and using computers to construct images of the bowel mucosa in two and three dimensions, with other enhancements to assist in interpretation [11].

Current guidelines for colorectal cancer screening

In May 2018 the ACS revised its colorectal screening guidelines, advising that regular screening for people at average risk start at age 45 years. ACS recommendations include the following: for people in good health and with a life expectancy of more than 10 years, regular colorectal cancer screening should continue through to the age of 75. People aged 76 to 85 should make a decision with their medical provider about whether to continue screening, based on their own personal preferences, life expectancy, overall health, and prior screening history. People over 85 should discontinue

Table 1. *Screening tests for colorectal cancer (gFOBT=guaiac-fecal occult blood test, FIT= Fecal Immunochemical Test).*

TEST	ADVANTAGES	DISADVANTAGES
gFOBT	No danger for the colon No bowel preparation needed Cheap Easy to perform at home	May not detect present polyps or tumors May be false positive Performed once a year (if normal) Diet and/or medication adjustments required prior to the test Any abnormal finding should be followed up with a colonoscopy
FIT	No danger for the colon No bowel preparation needed Cheap Easy to perform at home No diet and/or medication adjustments required prior to the test	May not detect present polyps or tumors May be false positive Performed once a year (if normal) Any abnormal finding should be followed up with a colonoscopy
Stool DNA Test	No danger for the colon No bowel preparation needed Easy to perform at home No diet and/or medication adjustments required prior to the test	May not detect present polyps or tumors May be false positive More expensive than other fecal tests Performed every three years (if normal) Any abnormal finding should be followed up with a colonoscopy
Flexible sigmoidoscopy	Safe and fast Sedation usually not required No bowel preparation required Performed every 5 years (if normal)	Does not visualize the whole colon May not detect polyps Uncomfortable for the patient Small risk of hemorrhage, infection or colon rupture Any abnormal finding should be followed up with a colonoscopy
Colonoscopy	Allows visualization of the whole colon Allows Biopsies and polyp removal Detects other possible abnormalities Performed every 10 years (if normal) The most reliable of all the CRC screening tests	Bowel preparation required Sedation may be required May miss small polyps More expensive than other tests Patient might miss a work day Small risk of hemorrhage, infection or colon rupture Uncomfortable for both doctor and patient
CT colonography	Safe and fast Usually visualizes the whole colon No sedation required Performed every 5 years (if normal)	Not widely available May miss small polyps Bowel preparation required Some false positive results Exposure to radiation Does not allow biopsies or polyp removal Any abnormal finding should be followed up with a colonoscopy

colorectal cancer screening. In addition, individuals with family history of colorectal cancer or polyps, family history of a hereditary colorectal cancer syndrome such as Familial Adenomatous Polyposis (FAP) or Hereditary Non-Polyposis Colon Cancer (HNPCC), personal history of colorectal cancer and personal history of chronic in-

flammatory bowel disease (ulcerative colitis or Crohn's disease) should undergo colonoscopy at an earlier age and more frequently than average risk individuals [13].

The updated guidelines on colorectal cancer screening by the American College of Gastroenterology (ACG) published in March 2021 in the American Journal of Gastroenterology recommend CRC screening in average-risk individuals between the ages of 50 and 75 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC. They also suggest CRC screening in average-risk individuals between the ages of 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC. Finally, they suggest that a decision to continue screening beyond age 75 years be individualized, with colonoscopy and FIT as the primary screening modalities [14].

Current guidelines of the European Society of Medical Oncology (ESMO), with which a Pan-Asian panel of experts agreed and 'accepted' completely (100% consensus), recommend a complete colonoscopy for CRC screening in average-risk men and women based on higher sensitivity and specificity when compared to other tests. The optimal age range for testing is 50-74 with an optimal repetition interval for a negative test of 10 years. Flexible sigmoidoscopy (FS) carried out every 5-10 years may be an alternative for those who refuse colonoscopy. The combination of this method with a yearly FOBT is recommended to reduce the risk of a right colon tumor. Other invasive tests including capsule colonoscopy are not recommended for screening. Non-colonoscopic tests are recommended in average risk men and women from the age of 50 not already taking part in colonoscopic screening programmes. The optimal frequency of testing is every year and no later than every three years. A colonoscopy must be carried out at the earliest convenience when the test results are positive. Among the available tests, FIT appears to be superior to high-resolution gFOBT with respect to the detection rate and positive predictive value for adenomas and cancer. Individuals with a medical history of adenoma, colon cancer, inflammatory bowel disease (Crohn's disease and ulcerative colitis), significant family history of CRC or adenoma, or an inherited cancer syndrome (2%-5% of all CRC), such as familial adenomatous polyposis coli and its variants (1%), Lynch-associated syndromes (hereditary non polyposis colon cancer) (2%-4%), Turcot, Peutze-Jeghers and MUTYH-associated polyposis syndrome, are considered to be at high risk for developing colon cancer and must be actively screened and in case of inherited syndromes, also referred for genetic counseling [15].

Barriers to colorectal cancer screening

Despite current guidelines and strong evidence that screening for CRC reduces incidence and mortality, the international screening for CRC uptake remains low in comparison with other screening methods such as mammography for breast cancer screening, a smear test for cervical cancer screening and PSA screening for prostate cancer [16]. CRC screening prevalence is below the national target in the USA. In 2018, 68.8% of adults were up to date with CRC screening. The percentage up to date was 79.2% among respondents aged 65–75 years and 63.3% among those aged 50–64 years. CRC screening prevalence was lowest among persons aged 50–54 years (50.0%) and increased with age [17]. An analysis of different programs in several European countries showed differences in screening participation rates, which in some countries (Croatia and Czech Republic) was lower than 30%. The same analysis showed that general participation rates in different programs globally currently exceed the acceptable minimum of 45%, but they have not reached the desired target (> 65%) [18].

Several studies have tried to identify the reasons behind low participation in CRC screening programs. By understanding the factors associated with CRC screening compliance, we may influence them and alter them. A systematic review by Wools et al, showed that frequently reported barriers for CRC adherence include female gender, age less than 65 years, low education level, low income, lack of health insurance, lack of awareness or the fear that the test might be painful or unpleasant, and ethnic minorities. On the other hand, prior experience of screening, dealing with a chronic disease, a family history of CRC, regular doctor visits and recommendation to start screening for CRC by their personal physician appear to be facilitators of CRC screening adherence [19]. Another recent systematic review by Dressler et al, found a range of barriers and facilitators of CRC screening, which could be divided into the following themes: psychology (e.g. forgetfulness, disgust for certain tests), religion, logistics (e.g. lack of time, other priorities, worries for test costs), health-related issues (e.g. mental issues), knowledge and awareness (e.g. absence of bowel related symptoms), general practitioner (support by a primary care physician) and environmental (e.g. social encouragement for participation) factors [20]. Several suggestions for increasing participation rates in CRC

screening programs have been made in the literature, including bigger involvement of general practitioners, implementation of media campaigns, an active call-recall system and systematic reminders to both patients and physicians [20,21,22].

The role of primary care

During the last few years, the role of primary care physicians (PCPs) in the prevention, diagnosis, and management of a number of benign and malignant gastrointestinal disorders has been recognized as very important. The role of PCPs becomes even more significant in the case of CRC as, with suitable screening programs, the rate of this neoplasm could be diminished markedly. Improvement in CRC screening rates largely depends on the efforts of PCPs to implement effective systems and procedures for screening delivery [21]. One of the key roles of PCPs currently recognized in CRC screening is to provide information to patients for their choices and decision making on screening, and it seems that PCPs' personal involvement results in better rates of participation in CRC screening programs [19,21]. The unique patient-physician relationship in primary health care, in terms of trust and continuity of care, can effectively contribute to patient compliance [23].

Although the contribution of PCPs to colorectal cancer prevention is undoubtedly important, it remains inadequate in many cases. Both PCPs and average-risk adults have identified lack of patient awareness and physician recommendation as key barriers to obtaining CRC screening. It is very important to identify the causes of this phenomenon. Probably a major reason for that is that many PCPs do not adequately follow CRC screening guidelines [21]. Several studies have demonstrated a lack of adequate knowledge regarding CRC screening among health care providers in both developed and developing countries, and suggest it could be one of the major barriers that need urgent attention [24,25]. A study by Mauri et al, found that CRC screening is recommended by 65–95% of PCPs in Europe, but the majority of them implemented it only among high-risk individuals, with FOBT advised by 42–83% and prescription of screening endoscopic modalities being inconsistent [26]. In Greece, a study by Kamposioras et al, found a wide variety of screening recommendation habits among primary care physicians, with non-recommended tests being frequently advised [27]. Available data indicate that a large effort is required to persuade PCPs to consider CRC screening programs as a very important part of their clinical practice [21]. Additional factors that are often reported as obstacles in CRC screening by PCPs include lack of training, not having adequate time for a stool test during a consultation, not finding screening to be effective, and a difficulty in persuading patients who had no signs of colorectal disease to participate in screening programs [22,23].

It is evident, then, that a number of actions should take place, so that primary care can have a bigger, more positive impact on increasing CRC screening adherence. Better training of PCPs on CRC screening, prevention and counseling techniques should be a priority [23]. Strategies that could be considered include integrating targeted efforts to address the deficiencies in curricula used to train nurses and PCPs, increasing access to continuing professional education programs focusing on cancer prevention and screening, and access to evidence-based protocols and guidelines about CRC screening in clinical practice settings [24]. Also, since communication skills and the doctor–patient relationship are very important in this process, the vocabulary that a doctor uses while delivering the test and the choice of when to suggest the screening should be explored [22]. A more comprehensive discussion of CRC screening can increase the rates of CRC screening and PCPs must always answer the patient's personal questions with clarity to avoid any misunderstanding. They should also be flexible in their suggestions by changing to or adding another screening modality when required [21,22]. There have also been suggestions for better health care system organization in several countries with low CRC screening participation. Countries like the UK have chosen a national organization of CRC screening, operating through a call and recall system, sending out test kits, analyzing samples and dispatching results. Such a centralized system puts less pressure on the individual organizational capacities of PCPs and can help overcome many of the difficulties mentioned for both PCPs and patients [22,23,28].

CONCLUSIONS

Despite current guidelines and screening success in the prevention of CRC, public awareness and participation in CRC screening programs remains below the desired targets. PCPs can play a major part in modifying patient adherence, and thus should be constantly up to date with recent CRC screening recommendations,

while also improve their communication skills and be ready to address any patient questions and problems. Continuing training of PCPs and improvement of primary health care systems are measures that can have a positive impact on public participation in CRC screening programs.

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COVID-19 crisis – It is time for doctors to act as managers. Conceptualizing the experience in a Greek Radiation Oncology Department

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Abstract

The current COVID-19 pandemic has incited us to investigate the possibility of applying managerial changes to effectively deal with this health crisis within a Radiation Oncology Department in Greece.

We performed a literature review using the MEDLINE and PubMed databases up to July 2021, identifying the most relevant papers containing the keywords "COVID-19", "management crisis" and "leadership". We also analyzed the number of cancer patients referred for treatment to our Hospital and to our Department during the years 2019, 2020 and during the first quarter of 2021.

We propose a four-level plan of action to effectively manage this crisis, based on data derived from management theories and leadership. There was not a statistical difference in the number of patients referred and treated between years 2019 and 2020, as the measures taken did not affect the daily practice of the Department.

The COVID-19 pandemic has offered us the opportunity to review working practices and to realize that proper planning and prioritization of needs are important factors for the ordinary exercise of medicine. It revealed the potential of remote consultations in the context of telemedicine which, after careful assessment of its potential, could be considered as the modern revolution in medicine.

Key words: *COVID-19; health crisis; radiotherapy; management*

INTRODUCTION

The COVID-19 pandemic poses an enormous challenge not only for the Health Sector worldwide, but also for societies and national economies across the globe. This pandemic caused a crisis, which urged all Health Systems to abandon conventional practices and cope with the prevention of this infectious disease, its treatment, and the rehabilitation of infected patients, by utilizing **all available** resources. This health crisis is exaggerated by the fact that it is presently difficult to predict its duration. Many researchers have issued guidelines for the management of patients with COVID-19, focusing mainly or exclusively on the medical treatment of these patients in the hospital environment.

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The word "crisis" originates etymologically from the Greek word "*κρίσις* (krisis)", which means judgement, choice, or decision [1]. The use of the term, however, varies depending on the context in which it is being used and the researcher's discipline [2].

When we refer to health crisis management, we imply that a coordinated and effective operational action plan of certain groups of people exists and is implemented in case of imposed threat to civilians' health and health systems, regardless of cause and extent [3]. As a matter of fact, very few publications are dealing with management challenges caused by this crisis, in terms of management perspective, whilst, alarmingly, two recent publications assert that Health Systems have been wholly unprepared for this crisis [4,5].

This health crisis constitutes a challenge for any kind of health unit and especially for Radiotherapy ones, due to the peculiarities surrounding the treatment of oncology patients. The main concerns are mitigating the pandemic effects and ensuring the smooth provision of services.

The keys to success in a management crisis are good preparation, flexibility, having accurate data and demonstrating willingness to establish and implement the right measures by all the members of the department [6].

Consolidation management essentially includes all the measures and administrative policies that are chosen to be implemented for the organization to recover and return to a normal course. The consolidation manager must possess certain qualities, according to Hess et al. The most crucial ones are thinking in a systematic way and being willing to deal with any situation at hand [7]. This crisis has the characteristics of a life-threatening change to human environment, a high degree of uncertainty and the need for critical and potentially irreversible decisions [8]. Each of these phases differs in its content, duration, and management opportunities.

This study's aim is to review all available literature on the management of the COVID-19 pandemic as a crisis, focusing on management guidelines. Then, based on these guidelines, the aim is to describe the actions taken in a small-sized Radiation Oncology Department within a tertiary public Hospital**.**

MATERIALS AND METHODS

A comprehensive search of the MEDLINE and PubMed databases was undertaken for the period December 2019 until July 2021, with the following terms: COVID-19 AND management crisis (6 articles) /AND radiation oncology (912 articles) OR radiotherapy (613 results) / AND leadership (1101 articles), along with guidelines on COVID-19 and radiotherapy published by the ESTRO and ASTRO Societies (www.astro.org, www.estro.org).

A total of 2 articles were found to fit the search COVID-19 AND management crisis AND radiation oncology AND leadership [9,10].

We analyzed the number of new patients treated in our Department for every month, for the calendar years 2019, 2020 and the first quarter of 2021. We also calculated all new referrals to the Department and the number of patients diagnosed with cancer in our Hospital for the years 2019 and 2020.

RESULTS

Based on available literature, we propose a "four level" action plan set to assist the doctor in acting under the capacity of a health crisis manager. The ways to address the current crisis can be included in this "four level" action plan and the proposed pandemic mitigation measures have been implemented in the Unit since March 2020 (Table 1).

Analysis of our data revealed that the average number of patients treated per month for the year 2019 was 55.6 ± 7.8, for the year 2020 52 ± 12.7 and for the first four months of 2021 it was 59.25 ± 11.18. The variables were examined for regularity by Kolmogorov-Smirnov and Shapiro-Wilk tests and it was found that they follow a normal distribution. Data processing does not show a statistically significant correlation between the years 2019 and 2020 ($p = 0.189$), although during the first lockdown imposed in Greece between March and May 2020, we observed a temporary decrease in the number of patients receiving radiotherapy. More precisely, this number was decreased by 22.4% for March, 39.1% for April and 31.4% for May. The Radiation Oncology Department accepted 676 new patients in 2019, while in 2020 this number was reduced by 4%, i.e., 648 new patients. The number of new patients with solid tumors and hematological malignancies who were diagnosed and / or treated at the University Hospital of Patras was 2773 for the year 2019 and 2519 for the year 2020, i.e., a decrease of 9.15% (Diagram 1).

DISCUSSION

Regarding the workflow of Radiation Oncology Departments during the COVID-19 crisis, all accessible literature focuses on two main topics:

Table 1. *Ways to address the pandemic can be included in four levels of action.*

A. Mobilization (Mobilize):	***B. Stabilization of the new situation (Stabilize):***
• Appointment of a person responsible for the implementation of all necessary measures indicated by the Health Authorities. • Implementation of measures for early diagnosis of infection and prevention in order to limit the possible spread of the virus in the Department (landscaping, change of examination and monitoring program (follow up) of patients, appropriate training of staff in hygiene issues, wide availability of antiseptics, reduction of seats in the waiting room, disinfection of spaces between treatments). • Redistribution of responsibilities to staff belonging to vulnerable groups (employees with chronic diseases such as immune diseases) and implementation of telework, which in the case of the Department was not possible. • Due to the small number of staff of the Unit it is not possible to create "two teams", in case one member of one team is forced to be quarantined, the other team to continue to provide its services. This measure will be applied in case the number of infected increases excessively in the Hospital or in the community. • Reduction of the number of visits with physical presence in the Department: Selection of patients for the order of priority of starting treatment, modification of radiotherapy regimens (application of short-term regimens especially for patients undergoing palliative radiotherapy) according to the current guidelines and international scientific societies. • Evaluation of the early symptoms of COVID-19 infection and differential diagnosis from the malignant disease or the side effects of radiotherapy. • Strict control of the mobility of caregivers within the Unit and enforcement of the measure "one attendant per patient". • Interruption of educational procedures for undergraduate students.	• Meeting-discussion between the members of the Group on a daily basis, for the current information from the Infection Committee of the Hospital, recording the course of the disease of any patients and the treatment of emergency problems (e.g., infection of a patient or staff member, lack of personal protective equipment, assessment of the severity of emergencies). • Establishment of an "action scenario" in case of detection of a patient positive for coronavirus. • Establishment of a rapid test examination in all patients on the day of arrival for the first treatment and then once weekly. • Establishment of methods of remote counseling with patients and caregivers after the end of treatment. • Encourage the use of the internet and the telephone for the communication of patients-caregivers with the Department. • Contact with the COVID-19 Manager and the psychologist of the Hospital for the solution of emergency problems and mainly for the psychological support of the employees. • Assurance with the Medical Equipment Company (ELEKTA) that the periodic and emergency maintenance of the equipment will not be interrupted.
C. Strategy:	***D. Re-Normalize:***
• Evaluation of the measures taken and their evaluation in order to establish them as practices even after the escape of the pandemic. Especially distance communication and hypofractionation regimens • Security of personal data - network security (cybersecurity) • Cost reduction and supply improvement strategies	• The purpose is to gradually return to normal, which is currently not visible.

Generally applied medical guidelines

A basic priority is the prevention or mitigation of transmission forms among patients with cancer and the personnel. The guidelines produced by various Societies are presented in the publication of Mauri et al. [11].

Measures specific to Radiation Oncology Departments

Dinh et al. present specific guidelines applied in Radiation Oncology Departments regarding not only the mitigation of disease transmission, but also the applied practices in the Department in terms of patient treatment and care [12]. In a paper published by Hinduja et al. from India, the finer details associated with running a Radiation Oncology department in times of a pandemic are presented [13].

But the key issue for Radiation Oncology Department remains treatment priority that should be given to cancer

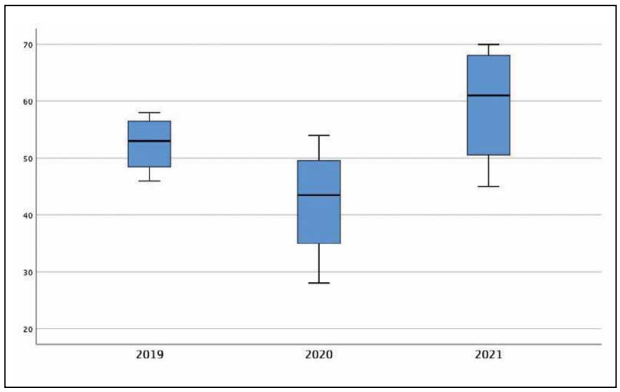

Diagram 1. Statistical data from the Radiation Oncology Department for the years 2019, 2020 and first quarter of 2021. Number of patients treated monthly.

patients according to the site and stage of the disease. Pandemics like the one caused by COVID-19 raise not only medical questions which cannot always answered by the data from evidence-based oncology, but also ethical dilemmas because of limited resources and increased risks of infection. Simcock et al. presented a simple model for the harm associated with COVID-19 infection in cancer patients [14]. They concluded that although colleagues around the world have dealt with enormous service pressures in the face of natural disaster or infections previously, the global scale and challenge of COVID-19 is unprecedented. For radiation oncology, this includes best practices from frameworks used successfully in other crises, published evidence, and international input. In line with previous recommendations, we urge units to proactively prepare their departments with training and Personal Protection Equipment and evaluate their infection control procedures. Departmental agreements on adapting remote working practices and hypofractionation regimes (or even avoiding or delaying treatment) are likely to reduce the burden of this disease on our cancer population. It is worth to mention here that the delay in offering radical or adjuvant radiotherapy, is associated with increased mortality for breast, head and neck and cervix cancer patients [15]. The use of social media has proven a very effective method of colleagues globally networking and sharing insight and experience.

COVID-19 as a management crisis in a Radiation Oncology Department

The term "crisis" is characterized as "high consequence, low probability, overlaid with risk and uncertainty conducted under time-pressure, disruptive of normal business and potentially lethal to organizational reputation", according to Ann Gregory [16]. Additionally, by way of definition, "public health crisis" is a sequence of events affecting humans in one or more geographic areas, following a public health threat, with limited time available for deciding and a large degree of uncertainty leading to the limitation of normal response capacity. Health crises generally have significant impacts on community health, loss of life, and on the economy. Its severity is often measured by the number of people affected, by its geographical extent, or death rate of the pathogenic process from which it originates. Synonym to that is "public health emergency", which according to WHO [17] is defined as "an occurrence or imminent threat of an illness or health condition, caused by bio terrorism, epidemic or pandemic disease, or (a) novel and highly fatal infectious agent or biological toxin, that poses a substantial risk of a significant number of human facilities or incidents or permanent or long-term disability".

Historically, humanity has experienced several pandemics caused by infectious agents in the last 100 years: The Spanish flu in 1918, the HIV/AIDS in 1981 till today, the "Swine flu" or H1N1/09 pandemic in 2009 and the recent SARS-CoV epidemic.

In their publication Begun and Jiang introduce the concept of "Complexity Science", which views health care delivery organizations as complex adaptive systems that operate in highly complex and unpredictable environments. They concluded that Complexity Science puts emphasis on simple rules, open discussions and building connections and provides an orienting framework for response to major surprise [18].

Ways to address the current crisis (pandemic), to overcome the obstacles on patient's health and disease prognosis can be summarized in the following plan of action (Figure 1, Table 1):

A. Mobilization (Mobilize): According to Watkins and Bazerman, the rationale for dealing with a crisis is to identify the emerging threat in a timely manner, prioritize it and mobilize it quickly by means of effective measures [19]. At this stage the aim is to react and adapt quickly to the new data.
B. Stabilization of the new situation (Stabilize): The affected Organization is now faced with a crisis,

Figure 1. Illustrative presentation of the COVID-19 crisis.

but with the proper preparation and implementation of the appropriate measures taken, it succeeds in stabilizing itself in this new situation and then, after a "x" period, it can achieve a gradual return to normality. The aim at this stage is to establish and strengthen the measures and practices introduced in the "Mobilization" phase.

C. Strategy (Strategize): During a crisis, the new environment is deemed unstable and highly changing, and the personnel is operating under tension, as well as pressure, but also uncertainty due to a lack of a clear perspective on the outcome. At this point, the implementation of a sound strategy is the most important tool for assessing the measures taken. The overall strategic objectives, which must be measurable and realistic, the identification of strengths and weaknesses of the organization as well as opportunities for threats from the external environment, as well as the overall action plan, are part of a coherent and operational-strategic planning [20]. The goal at this level was to redesign and develop an operational strategy for a successful transition to normalization.
D. Anti-aliasing (Re-normalize): The final phase of the crisis cycle in an Organization is normalization [21]. The objective of this step is the gradual return to normality, which is currently not visible.

The analysis herein will allow us to perceive this pandemic in terms of management and leadership and will help us to delimit the crisis in a more general content, whilst, simultaneously, measure more accurately the economic repercussions for the Health Sector. And most important, this analysis will assist Organizations in designing and establishing a "crisis-sensitive plan" with the support of health-policy makers.

The COVID-19 pandemic has currently gone into a catastrophic new chapter according to Johns Hopkins statistics (22). So far, a total of 245.092.869 people has been infected, while 4.973.610 have died (27 October 2021). Compared with COVID-19, the earlier epidemic of SARS and MERS was much slower in spreading around the globe. Increased globalization, international traveling, and virus adaptability in almost all countries without distinction are often reported as the primary reasons behind the rapid spread. The latter is also attributed to the risk assessment regarding COVID-19 virulence capacity. To date, there is no single specific therapeutic option for battling against this virus.

Considering the recent findings by Bardet et al. from France, diagnostic and treatment delays in patients with cancer, due to COVID-19, may have an impact on patient physical and mental health and on survival per se [23]. These delays, rescheduled or cancellation in radiotherapy, have been one of the main problems that oncological patients have faced. Due to the same reason, the post-treatment follow-up programs have also been affected. Consequently, to tackle the post lock down patient backlog, we have extended working hours in the Department and we continue to prioritize patients according to the diagnosis [24].

This crisis revealed the potential of remote consultations in the context of telemedicine which, after careful assessment of its potential, could be considered as the modern revolution in medicine. Telemedicine (telehealth) can provide remote support to patients thereby reducing physical access to the hospitals and costs [25,26]. Along with this technology facilitation comes Artificial Intelligence-based imaging analysis and health informatics for monitoring patients [27].

Telemedicine can be of great help in the management of patients who recovered from the infection but need rehabilitation. Salawu et al propose a model of tele-rehabilitation as an alternative to traditional face-to-face intervention [28].

It appears that almost twenty-two months after the start of the pandemic the operating system of the Radiation Oncology Department is in a stabilization phase and the effectiveness of all measures is becoming apparent. The time frame until full recovery to normality is certainly unknown at present and depends on four main variables: (a) the effectiveness of measures to reduce the spread of the virus, and in particular the vaccination program, (b) the effectiveness of budgetary and economic measures, (c) the ability of the health system to maintain and increase its ability to handle the volume of critically-ill patients, and (d) the timing of the availability of specialized medicinal products for the treatment of the disease. This study was conducted in one, medium-sized by Greek standards, Radiation Oncology Department and it is based on home statistics and relevant literature. In other words, the proposed plan of action is based on existing literature data and not on data accumulated during the crisis. We are planning to form a properly structured questionnaire among the personnel working in Radiation Oncology Departments at a national level, to identify the appropriate measures and practices adopted during a health crisis. Additionally, although all information included in this study must be interpreted in the context of the cur-

rent COVID-19 situation, it can be of a great assistance for resolving future health crisis caused by a natural disaster, terrorism, or a new pandemic. It is important to organize in the Department a "Network of Teams" which can serve common purposes such as workforce protection, operation of the treatment machines (linear accelerators) and prompt communication with patients and their caregivers.

CONCLUSIONS

This pandemic has presented us with challenges that we have not been exposed to so far. For the personnel of Radiation Oncology Departments, the rule "Do not cancel treatments" has been applied. This crisis strengthened the group's links and redefined the concepts of collective and individual responsibility. It has granted us the opportunity to review working practices and realize that proper planning and prioritization of needs are important factors for the safe exercise of medicine.

An important parameter in everyday practice was the introduction of telemedicine, aiming at reducing the exposure of patients and staff by face-to-face appointments. Although this adjustment under COVID-19 will continue, we must be reluctant to move to its routine use without careful patient selection. We must consider multiple parameters ensuring that we maintain effective and safe healthcare to our patients.

Strong leadership, quality communication and clear direction are required during this crisis to ensure that radiation therapists receive all necessary support and resources required to maintain their safety and patient's well-being during the COVID-19 pandemic.

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An unusual presentation of cervical tuberculous lymphadenitis in a young man

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Abstract

Cervical lymphadenitis constitutes a common clinical entity with a broad spectrum of diseases in its differential diagnosis. Among several benign and malignant diseases, patients suffering from tuberculosis can manifest such a clinical presentation. In this study, we report an unusual case of tuberculosis in a 27-years old male of African origin, previously healthy, who was presented with a solid neck mass without any other associated features of the disease. Laboratory work up revealed the diagnosis of mycobacterial tuberculosis. Although disseminated mycobacterial lymphadenitis is rare in immunocompetent patients, this case highlights the need for clinicians to include tuberculosis in the differential diagnosis of cervical lymphadenopathy.

Key words: *Scrofula; tuberculosis; cervical lymphadenitis*

INTRODUCTION

Cervical lymphadenopathy remains for clinicians a diagnostic dilemma as it can be part of the clinical presentation of several benign and malignant diseases. Tuberculosis (Tb), with its several forms of manifestation can affect both immunocompromised and immunocompetent patients, leading to increased morbidity and mortality rates. The incidence of tuberculosis is currently increasing worldwide and tuberculous cervical lymphadenitis, the most common presentation of extra-pulmonary Tb, should be considered in the differential diagnosis of cervical lymphadenopathy [1,2,3]. Herein, we present the case of a 27-years old previously healthy African male, with a one month- long history of progressive left neck swelling but no other symptoms. Physical examination was not indicative of the disease but the culture and the polymerase chain reaction (PCR) of the specimen of the neck lymph node confirmed the diagnosis of Tuberculosis.

CASE PRESENTATION

A 27-years old male from Africa, resident in a refugee hospitality center, was referred from a local medical centre to the Emergency Department of the University Hospital of Patras, Western Greece, for further investigation of a left-sided cervical lymph nodes swelling. This clinical finding had progressed for over a month. Our institution does not require ethical approval for reporting individual cases.

Upon admission, the skin cervical swelling was not red, warm or tender and the patient did not mention swelling elsewhere. No concomitant symptoms such as weakness, convulsions, weight loss, sweating and fever were reported. The rest of the physical examination was unremarkable, the patient was hemodynamically stable and respiratory competent. He had no thoracic auditory findings, as well as no splenomegaly or liver

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enlargement. No abnormal findings from bilateral eye ophthalmoscopy were noticed. The patient had received amoxicillin/clavulanic acid (1 gr bd po) in combination to clarithromycin (500 mg od po) for 20 days prior to admission without any clinical improvement.

Serology for Influenza A and B, Parvovirus B19, EBV and CMV, ECHO virus, Coxsackie virus, HSV, VSV, and Adenovirus*, Coxiella burnetii, Chlamydia, Leptospira spp.,* and HIV were negative. Previous HBV infection [anti HBs Ab: 36.24 mUI / ml (+) (reference rates: <10 mIU/ml negative), anti-Core IgG: 4.53 (+) (reference rates: >1 positive)] was confirmed from serology results. The rest of the patient's laboratory findings during hospitalization are presented in Table 1. The tuberculin skin test, was read 3 days after placement, was blistered (10x15 mm) with an additional 30x40mm of surrounding in duration.

The chest X-ray was normal. A contrast enhanced Computed Tomography (CT) of the neck demonstrated multiple abnormalities of the left cervix such as scared enlarged cervical nodes, some with central necrosis and peripheral enhancement (figure 1). There was no inflammation or abnormal findings of the surrounding soft tissues and chest.

The neck lesions were punctured under CT guidance and then the patient started treatment with an antifungal agent [fluconazole 400 mg once daily (od) intavenously (IV)] combined with ciprofloxacin [400 mg twice daily (bd) IV] according to the instructions of the Infectious Control Consultant team of the Hospital. Pathologic and cytologic examination of the puncture material were not specific and showed no evidence of malignancy. Although no lymphadenoid tissue

Table 1. *Patient's laboratory tests.*

	Admission Day	Discharge Day	Reference rates (Units)
WBC	4,61	3,80	4,0 – 11 K/ml
RBC	4,92	4,59	4,2 - 6,2 M/ml
Hematocrit	44,00	41,10	36,0 - 52,0 mg/dl%
Hemoglobin	15,00	13,70	11,8 - 17,0 g/dl
PLT	334,00	257,00	150 – 400 K/μl
Glucose	88	78	75 – 115 mg/dl
Sodium	134,0	139,0	134 – 152 mmol/l
Potassium	4,5	4,3	3,8 - 5,5 mmol/l
Urea	14	27	15 – 54 mg/dl
Creatinine	0,8	0,8	0,9 - 1,6 mg/dl
SGOT	34	29	5 – 40 U/l
SGPT	24	16	5 – 40 U/l
ALP	71	77	34 – 104 U/l
LDH	329	249	120 – 230 U/l
γGT	21	25	10 – 50 U/l
CPK	56	58	< 190 U/l
CRP	3,18	2,03	>0,80 positive
Total Bilirubin	0,53	0,64	0,1 - 1,3 mg/dl
Albumin	4,3	3,9	3,5 - 5,5 g/dl
Amylase	82	102	10 – 220 U/l

Abbreviations: Tb: Tuberculosis; WBC: white blood cells; RBC: red blood cells; PLT: platelets; SGOT: serum glutamic- oxaloacetic transaminase; SGPT: serum glutamic- pyruvate transaminase; ALP: alkaline phosphatase; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; γGT: gamma- glutamyl transferase; CRP: C- reactive protein; AFB: acid-fast bacilli; EP: emergency physicians; od: once daily; IV: intravenously; bd: twice daily, td: three times daily.

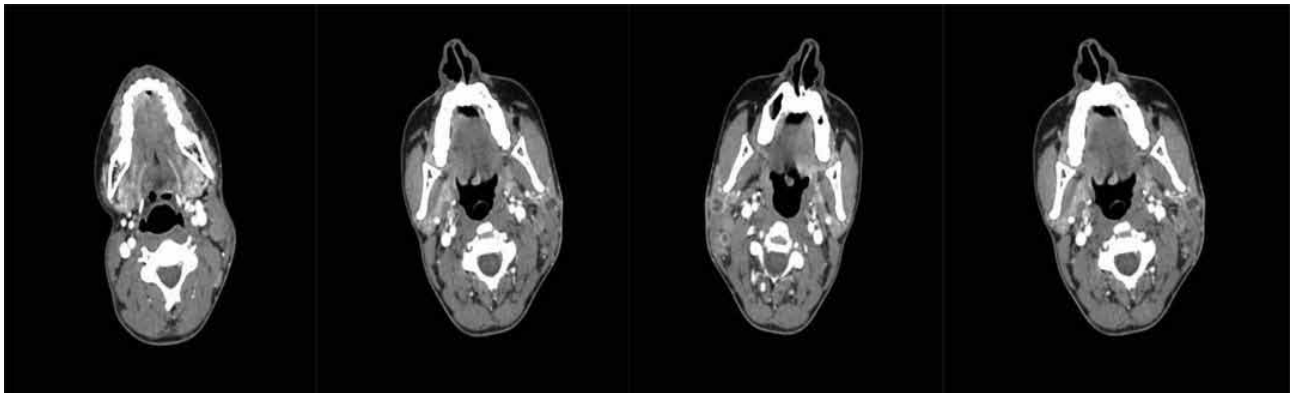

Figure 1. CT scan of the neck showed multiple abnormalities of the left cervix such as scared enlarged cervical nodes, some with central necrosis and peripheral enhancement.

was detected in the histological preparation, the skin fragment and underlying fat produced evidence of chronic inflammatory infiltration. A Ziehl-Nielsen stain for acid-fast bacilli (AFB) was negative but culture as well as PCR of the lymph node material were positive for *Mycobacterium Tuberculosis* complex. Images of the cytologic examination of the specimen are presented in figures 2 and 3.

Based on the above, the patient was started on anti-tuberculous treatment consisting of pyrazinamide [500mg po three times daily (tds)], ethambutol (1250 mg po od), rifampicin (600 mg po od) and isoniazid (300 mg po od) for two months and then completed treatment with isoniazid and rifampicin for 4 additional months. The patient was discharged after 8 days of anti-Tb treatment. On one month's follow up, the patient remained symptom-free, in a good clinical status, with an extensive reduction in lymph node swelling.

DISCUSSION

We present the case of a 27-years old immunocompetent man with cervical lymphadenitis in whom tuberculous lympadenopathy was diagnosed. Disseminated lymphadenopathy represents a challenge to the majority of physicians with a wide range of differential diagnosis including both benign and malignant diseases, such as sarcoidosis, metastatic disease, hematologic malignancies and, although rarely present, tuberculosis [4-7]. In adults, 95% of cases caused by *Mycobacterium tuberculosis* are best treated with pharmacologic therapy [8-12]. In contrast, in paediatric cases of mycobacterial cervical lymphadenitis, 92% of cases are caused by non-tuberculous mycobacterium and respond best to surgical treatment [8, 13-15].

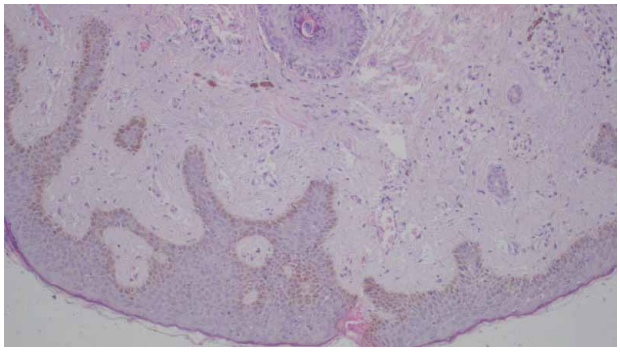

Figure 2. Hyperpigmentation of the epidermis. A few melanophages in the dermis.

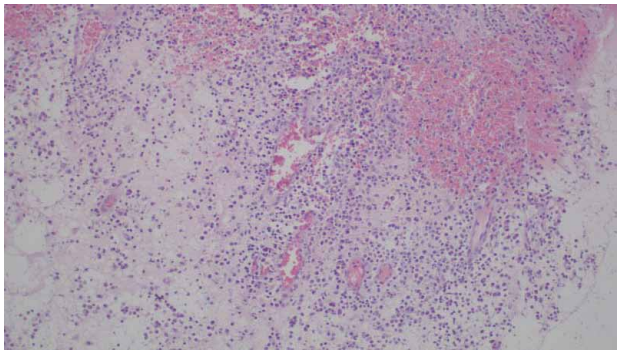

Figure 3. Mixed inflammatory infiltration of the subcutaneous tissue.

Tuberculosis is a major public health issue in Europe with 285,000 cases recorded in recent epidemiological surveillance. In terms of clinical presentation, 20% of cases were related to extra pulmonary tuberculosis. Of these, the most frequent location is the cervix [5,6] and is usually manifested by lateral lymph node enlargement in the cervix, which is often dorsal [7,8]. Tuberculous lymphadenitis has been seen in nearly 35% of extrapulmonary tuberculosis which constituted about 15 to 20 % of all cases [9].

Scrofula is a local manifestation of systemic disease. Scrofula, historically known as the "King's evil" in Europe, is a form of cutaneous tuberculosis [16]. The term «pig» (scrofula) has prevailed due to the similar appearance of pig skin in the affected area. It is a manifestation of systemic Tb disease, but more often, a separate entity located only in the neck. In the absence of systemic tuberculosis, unpasteurised milk may be the source of organisms that enter through breaks in the oral or tonsillar mucosa, causing regional lymph node involvement [17]. It may occur during primary tuberculous infection or as a result of reactivation of dormant foci or direct extension from a contiguous focus. Lymphatic vasculars drain the bacilli to the hilar lymph nodes. From the regional nodes, the organism may continue to spread via the lymphatic system to other nodes or may pass through the nodes to reach blood stream, from where it can spread to virtually all body organs. Scrofula most commonly affects individuals during the second decade of life with female predominance (approximately 2:1 ratio) [18]. Scrofula is caused by *M. tuberculosis* and other species of mycobacteria. Treatment depends on the type of pathogenic microorganism: *M. tuberculosis* is treated as pulmonary tuberculosis, whereas when other mycobacteria are involved, the treatment of choice is surgical removal of the affected lymph node due to its high recurrence rate [13-15]. Systemic symptoms

are often absent in immunocompetent patients. Concomitant pulmonary tuberculosis occurs in fewer than 50% of cases of scrofula [19]. Despite being a common presentation, mycobacterial cervical lymphadenitis remains a diagnostic challenge because it mimics other disease presentations including solid organ malignancy, lymphoma, connective tissue disease and other infections such as brucellosis [3].

A number of diagnostic techniques are available for the diagnosis of tuberculous lymphadenitis. Imaging modalities such as ultrasound, CT or magnetic resonance imaging (MRI) of the neck are often used for the initial evaluation of lymphadenopathy. Fine-needle aspiration of the affected lymph nodes is the preferred diagnostic procedure due to its relative ease, minimally invasive nature and cost-effectiveness [20]. Excisional biopsy has the highest sensitivity, while results of nucleic acid amplification tests are not reliable [19].

Cervical swelling is a common clinical problem with a complex differential diagnosis, which is a challenge for the clinician, at the emergency department as well as during inpatient investigation. Diagnosing scrofula is extremely difficult because it requires a high degree of suspicion. Although scrofula is generally rare, it is a clinical entity that we may encounter and should be able to recognize as emergency physicians (EP) working with indigents, immigrants, and immunocompromised patients. Missing a diagnosis of scrofula is indeed a missed opportunity to diagnose a patient with pulmonary Tb [21]. Without the availability of purified protein derivative (PPD) results, acid-fast bacilli (AFB) results, and culture results for TB, we must rely mainly on the history and physical examination to make the diagnosis [21].

Tuberculosis may present with a wide range of symptoms and its diagnosis remains challenging as it is difficult to establish it with clinical findings alone. For the diagnosis of a mycobacterial infection, it takes at least 2 weeks to have a positive culture from lymphadenic material and also it generally takes 6-8 weeks until a culture is considered negative for *M. tuberculosis* [6,12,22]. In our case, the patient may had a benefit from the quick induction of treatment for *M. Tuberculosis*, despite the poor clinical findings on admission. In our patient, scrofula was suspected despite the absence of tuberculosis findings from the lungs, due to the positive Mantoux test and the fact that in the patient's country of origin, tuberculosis remains a major problem [22]. The diagnosis of tuberculosis was confirmed from the identification of *M. tuberculosis* in the lymph node material, through cultures and the PCR. Patient was immediately started on anti - tuberculosis treatment, since the disease had been suspected.

CONCLUSION

In conclusion, the diagnosis of scrofula is quite difficult for clinicians (only 3 cases of scrofula in adults have so far been published in Greece) and requires a high degree of suspicion [23]. This clinical entity should always be considered in the diagnosis of cervical enlargement, especially when epidemiological criteria are raising the index of suspicion, even in the absence of constitutional symptoms. The diagnostic investigation of this entity is of great importance due to the high mortality of disseminated tuberculosis and the curative potential of anti-tuberculosis medication. In other words, as long as Tb is prevalent, scrofula should remain in the differential diagnosis of any unexplained neck enlargement. [4,6,7,24].

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Author contributions: *BD: wrote this case report; DZ, OK and AT: treated the patient; MG: performed the pathologic and cytologic examination of the biopsy material; ML: wrote this case report; DV: critically revised this manuscript.*

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