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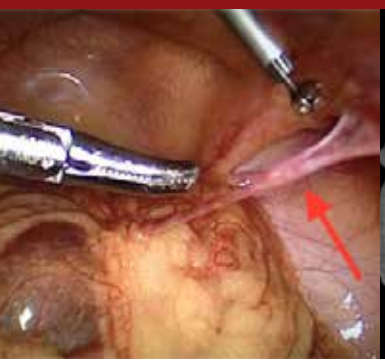
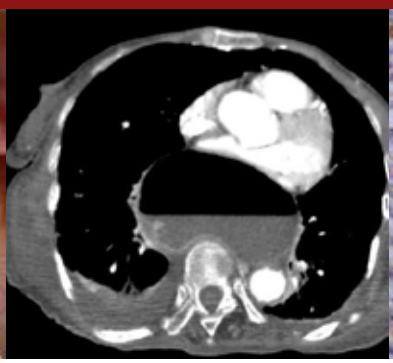
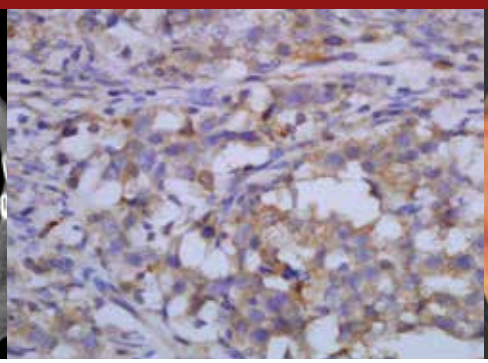
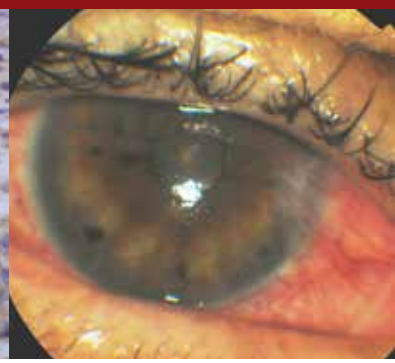

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Cyprus Journal of Medical Sciences (Cyprus J Med Sci) is the peer-reviewed, open access, international publication organ of Cyprus Turkish Medical Association. The journal is printed three times a year in April, August and December. The publication language of the journal is English.

Cyprus Journal of Medical Sciences aims to publish manuscripts at the highest clinical and scientific level on all fields of medicine. The journal publishes original papers, review articles, case reports and letters. Cyprus Journal of Medical Sciences is indexed in EBSCO.

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Editorial

Dear Colleagues,

Before I say a few words about our journal's latest developments, I would like to wish you all a healthy, successful, and happy life.

Our journal is now in its second year and is now publishing the first issue of the second volume. Very recently, we have been accepted by EBSCO. In this regard, I would like to thank EBSCO's executives, authors, referees, and the AVES Publishing. We have already applied for inclusion in ESCI and will subsequently apply for inclusion in other indices such as SCIE and PubMed. With your continued support, our journal's profile will continue to rise. By sharing your research results and ideas within our journal, important scientific contributions will be made in public health with regard to disease diagnoses and therapies.

I would like to mention the importance of peace in the continued success of scientific research. According to UNHCR data, more than 65 million people worldwide have been forced away from their homes as a result of wars and conflicts. This number includes nearly 21.3 million refugees, over half of whom are under 18 years of age. This situation causes public health challenges and triggers other problems for both refugees and hosting countries, including tragic drownings of thousands of refugees who attempt to flee their homes. We severely condemn the loss of life during recent terrorist attacks. Despite these challenges, I hope that peace will prevail and that we will be able to encourage the sharing of new scientific knowledge and research findings with our colleagues from all over the world.

Best regards,

Dr. Sonuç Büyük
Editor-in-Chief

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Original Article

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Primary Central Nervous System Lymphoma in Immunocompetent Patients: A Literature Review and the Experiment

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BACKGROUND
Primary santral nervous system (CNS) lymphoma is a rare form of non-Hodgin's lymphoma that develops within the craniospinal axis and causes less than 5% of all primary brain tumors. It is defined as lymphoma developing in the brain, leptomeninges, spinal cord or eyes without evidence of lymphoma outside the CNS. Clinico-histopathological characteristics of eighteen patients with primary CNS lymphoma were examined and followed-up for the treatment and subsequent management in Neurosurgery, and Medical Radiation Oncology.

MATERIALS and METHODS
This study includes all cases of primary CNS lymphoma diagnosed in our Department of Pathology between 2006 and 2009. Age, sex, clinical presentation and laboratory features analysis of the cases were carried out In addition, routine hematoxylin and eosin stains (HδE) and special stains, immunohistochemistry were carried out using CD-45 CD-20, CD-19, CD-3, CD-5, CD-10, MIB-1 and Bcl-6.

RESULTS
Primary central nervous system lymphoma (PCNSL) was mostly observed in the temporal and parietal and parietal region. The mean age of the patients was 57.72, ranging from 33 to 83 years. Females outnumbered males with a ratio of 1.25: 1. The most common symptom observed, was headache which was followed by neuro communicative symptoms. Histologically, all the patients exhibited diffuse B-cell lymphoma. Two patients suffered from multiple lesions. Three of the patients died within 2 years.

CONCLUSION
There is an increase in the prevalence of primary CNS lymphomas not only in immune defiency patients, but also in the immune competent patients and therefore should be taken into account in the differential diagnosis of all tumor of the CNS.

Keywords: Primary santral nervous system lymphoma, immunocompetent, brain tumor

INTRODUCTION

An uncommon type of non-Hodgkin's lymphoma, primary central nervous system lymphoma (PCNSL), is localized in the central nervous system. Most of its lesions are supratentorial and periventricular. Deep structures such as corpus callosum and basal ganglion are mostly involved (1-3). In this study, we analyzed 18 patients with non-Hodgkin's lymphoma in order to assess their clinical features, radiological features, histology, management, and outcome.

MATERIALS and METHODS

This study includes all the cases of primary santral nervous system (CNS) lymphoma diagnosed by our Department of Pathology between 2006 and 2009. Age, sex, clinical presentation, and laboratory features analysis of the cases were conducted. Details regarding lymphadenopathy, organomegaly, and bone marrow were acquired to rule out the possibility of secondary involvement of a systemic lymphoma (Table 1). In addition, routine hematoxylin and eosin (HδE) staining (Figure 1, HδE X10; Figure 2, HδE X20) and special stainings and immunohistochemical analysis were performed using CD-20 (Figure 3, X10; Figure 4, X20) CD-45, CD-19, CD-3, CD-5, GFAP (Figure 5) and antibodies for typing these lymphomas. CD-10, MIB-1, and Bcl-6 were also used for some cases. Eighteen cases of primary CNS lymphoma were diagnosed. All cases were analyzed for imaging features and followed up for management in Neurosurgery, and Radiation and Medical Oncology.

Data from microscopical analysis were expressed as mean±standard error. The statistical analysis was performed by using Statistical Package for Social Sciences version 22 software (IBM Corp.; Armonk, NY, USA).

This study was presented at the 27th European Congress on Pathology, 5-9 September 2015, Belgrade, Serbia.

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TABLE I. Descriptive characteristics distribution

		Min-Max	Mean±SD
AGE		33-83	57.72±14.36
		n	%
Additional diseases	No	12	66.7
	Yes	6	33.3
	Hypertension	3	16.7
	Cardiovascular disease	1	5.6
	Cardiovascular disease, Diabetes mellitus	1	5.6
	Cerebrovascular disease	1	5.6
Complication*	Headache	10	55.6
	Dizziness	3	16.7
	Amnesia	3	16.7
	Loss of consciousness	2	11.1
	Speech impairment	3	16.7
	Hemiparesis/paresis	6	33.3
	Epilepsy	1	5.6
	Central facial paralysis	2	11.1
Localization	Frontal lobe	1	5.6
	Frontal and parietal lobe	2	11.1
	Parietal lobe	3	16.7
	Periventricular	6	33.3
	Posterior fossa	1	5.6
	Supratentorial	3	16.7
	Temporal and parietal lobe	2	11.1
Stereotaxic biopsy		13	72.2
Excision		5	27.8
Radiotherapy	No	9	50.0
	Yes	6	33.3
	Ex	3	16.7
Chemotherapy	No	11	61.1
	Yes	4	22.2
	Ex	3	16.7

*Marked more than one option

Since the study was made from ready-made paraffin embedded blocks and slides in our lab archive, patient consent was not considered necessary.

Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

RESULTS

The study was conducted with a total of 18 cases diagnosed between 2006 and 2009. The age range of the patients was 33-83 years (average age was 57.71±14.36 years).

Six cases (33.3%) had additional diseases. Of the 6 cases, 3 had hypertension, one had cardiovascular disease, one had cerebrovascular disease, and one had cardiovascular disease and diabetes mellitus.

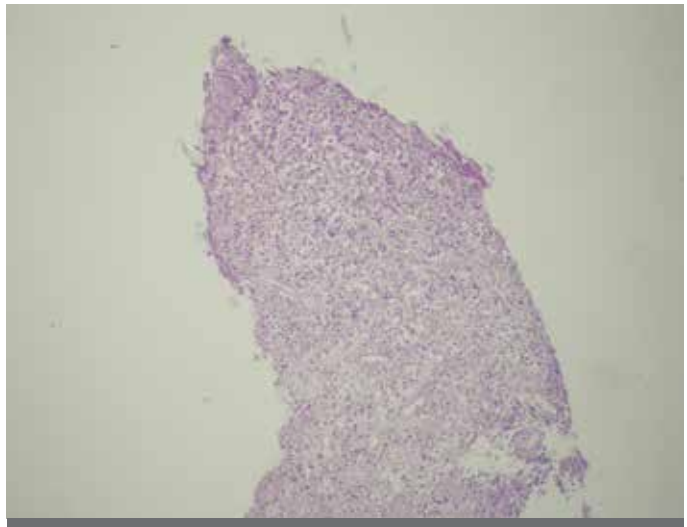

FIGURE I. H&E X10

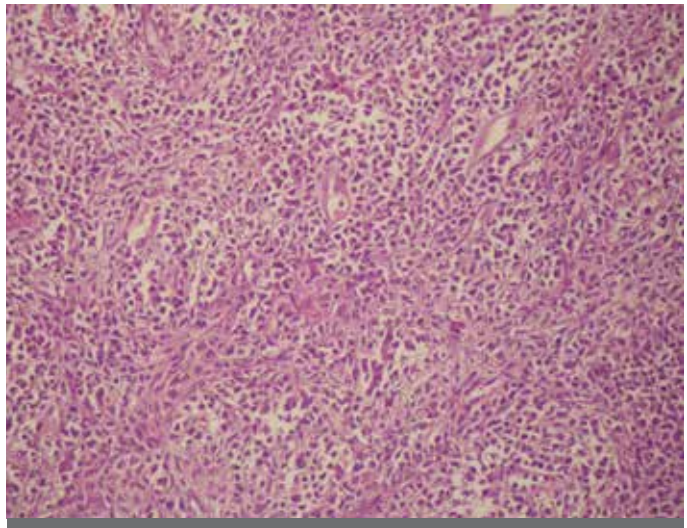

FIGURE 2. H&E X20

The analysis of the clinical symptoms indicated that 55.6% (10) suffered from headache, 16.7% (3) from dizziness, 11.1% (2) from loss of consciousness, 16.7% (3) from speech impediment, 33.3% (6) from hemiparesis/paresis, 5.6% (1) from epilepsy, and 11.1% (2) from central facial paralysis.

The analysis of localizations was conducted in all patients and 5.6% (1) frontal lobe, 11.1% (2) frontal and parietal lobe, 16.7% (3) parietal lobe, 33.3% (6) periventricular, 5.6% (1) posterior fossa, 16.7% (3) supratentorial, and 11.1% (2) temporal and parietal lobe localizations were observed.

Stereotactic biopsy was performed in 13 cases (72.2%) while excision was performed in 5 cases (27.8%). Radiotherapy was applied in 33.3% (6) of the cases, and chemotherapy was applied in 22% (4) of the cases. Death occurred in 16.7% (3) of the cases.

Microscopic features: Histopathology showed that most cases exhibited a monomorphic population of lymphoid cells with

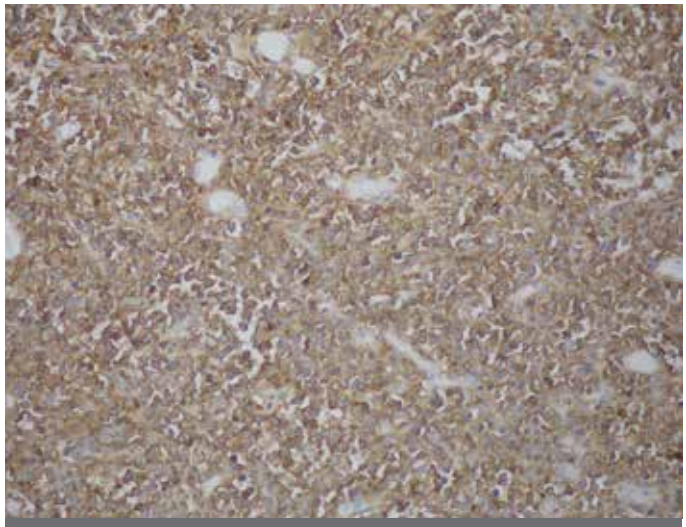

FIGURE 3. X10 (the tumor cells CD-20 positive)

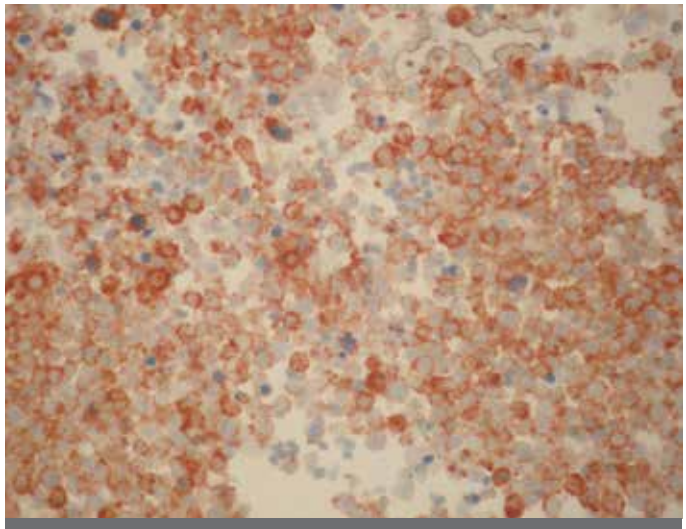

FIGURE 4. X20 (the tumor cells CD-20 positive)

areas of necrosis (Figure 1, 2). Individual cells were large with prominent nuclei.

Immunohistochemical profile: All cases were positive for CD-45, CD-19, and CD-20 (Figure 3).

Adjuvant Therapy

All patients were subjected to radio-chemotherapy after surgical decompression/stereotactic biopsy and histopathological/immunohistochemical diagnosis of lymphoma.

Follow-up was conducted jointly at the Tumor Clinic, which is managed by the Departments of Neurosurgery, Radiation Oncology, and Medical Oncology. Three patients died within 2 years. Four patients could not be followed up.

DISCUSSION

Primary central nervous system lymphoma is an uncommon tumor. The brain is an immunologically exclusive organ in the sense that it does not contain lymphatics or lymphoid tissue. Therefore, the origin of such a primary tumor is unclear. Hochberg et al. (4) argue that the clone of malignant systemic lymphocytes exhibiting distinct adhesion molecules and attaching themselves to certain proteins existing only in the CNS might be the pathogenesis.

FIGURE 5. X10 (the tumor cells GFAP negative)

The origin of PCNSL is quite unclear and therefore, it remains an obscure disease. One of the main risk factors of diseases such as PCNSL could be immunodeficiency-whether congenital or acquired. Farhangi et al. (5) report the case of a 2.5-year-old boy who suffered from autoimmune hemolytic anemia prior to PCNSL.

Studies indicate that there is a connection between Epstein Barr virus (EBV) and PCNSL in patients with HIV infection. However, no studies indicate a relationship between EBV and PCNSL in patients without HIV infection. The nature of the relationship between EBV and human lymphoma, whether it is causal or purely coincidental, remains a moot point (6). However, there has been an increase in the number of immunocompetent patients in the past few decades, and this increase has occurred independent of the developments in the field of neuroimaging or of the general aging of the population (7).

Brain biopsy remains the ideal technique for the diagnosis of PCNSL (8). High grade B-cell lymphomas comprise most of the PCNSL tumors, although a normal brain does not contain B-cells (9). The present case study is in accordance with the research conducted by Abla et al. (1) According to that study, diffuse large B-cell lymphoma (DLBCL) is the most prevalent form, while anaplastic large cell lymphoma (ALCL), lymphoblastic lymphoma, and Burkitt-like lymphoma are forms with lower prevalence. All 18 cases were B-cell lymphomas with positivity for CD-20 and CD-19.

Psychiatric symptoms together with focal neurological deficiencies are one of the several clinical indications that might be detected in PCNSL patients among other things (6). The analysis of the clinical symptoms indicated that 55.6% (10) suffered from headache, 16.7% (3) from dizziness, 11.1% (2) from loss of consciousness, 16.7% (3) from speech impediment, 33.3% (6) from hemiparesis/paresis, 5.6% (1) from epilepsy, and 11.1% (10) from central facial paralysis.

Considering the good response of CNS lymphoma to chemoradiation, PCNSLs are regarded as non-surgical tumors, and it has been reported that there is no use in undertaking resection or decompression since PCNSL exhibits a diffuse infiltration pattern and is mostly observed in deep-seated locations (2).

CONCLUSION

The distinctive features of our study were: primary CNS lymphoma was observed in immunocompetent persons; none of our patients were immunocompromised or HIV positive; and raised ICP features and focal neurological deficits were the most prevalent clinical manifestations.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: N/A.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Sodium Iodide Symporter Protein Expression and Clinicopathological Variables in Pure Testicular Seminomas

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BACKGROUND
Testis carcinomas cause cancer-related morbidity and mortality in adults. Radioiodine I-131 (RAI) therapy may be an alternative for the treatment. The aim of this study is to investigate the presence and localization of sodium iodide symporter (NIS) expression in pure testicular seminomas, two lymph nodes with seminoma metastasis, and two embryonal carcinomas by immunohistochemically methods.

MATERIAL and METHODS
The localization of NIS expression was defined as positive according to >10% membranous staining. Cytoplasmic staining was noted as present/absent. NIS expression was compared to the invasions.

RESULTS
There was no rete testis invasion in 66.7% (26/37) and epididymis invasion in 84.6% (33/37) of the cases. Lymphovascular invasion was seen in 64.1% (25/37) of the cases. There was no membranous staining in pure seminomas, but it was present in two embryonal carcinomas. Cytoplasmic staining was present in 41% (16/34) of the tumors. Cytoplasmic NIS expression was present in 72.7% (p=0.135) and 75% (p=0.6) of the rete testis and epididymis invasions, respectively. There was no statistically important relationship with the cytoplasmic expression, lymphovascular invasion, and the other parameters (p>0.05).

CONCLUSION
Research of NIS expression in pure seminomas with larger series may clear the option of RAI treatment in seminomas. Also, evidence of different expression profiles in non-seminomatous testicular tumors was determined.

Keywords: Adult, male, seminoma, testicular neoplasms, sodium iodide symporter expression

INTRODUCTION

According to Globocan 2012 data, the incidence and mortality of testis carcinomas in males are 0.7% and 0.2%, respectively. The five-year prevalence is 1.4% in adults (1). The incidences of germ cell testis tumors (seminoma/non-seminoma) were doubled every 30 years (2). Testis carcinoma cause cancer-related mortality and morbidity in adult males. Standard treatments of seminomas are radical orchiectomy, follow-up, adjuvant radiotherapy or chemotherapy (2). Although the treatment response of early-stage testis tumors especially seminomas is usually good, resistance may develop in a limited number of patients.

Although radioiodine I-131 (RAI) is primarily used for the treatment of thyroidal cancer, it is able to concentrate in extra-thyroidal organs like the breast, salivary glands, and the gastric mucosa (3). Also, a limited sodium iodide symporter (NIS) expression was determined in normal epididymis, testis, and prostate tissues (4). Therefore, RAI is considered an alternative method for the treatment of extra-thyroidal cancers. There are a few studies about NIS expression in normal testis tissue and testis tumors (5, 6).

Sodium ioidide symporter glycoprotein is necessary for the efficiency of RAI treatment as it is responsible for the iodine transport across the thyrocyte basal membrane. It is mentioned that NIS protein must be expressed in basolateral membranes of thyroid follicular epithelium in order to function (7, 8).

The aims of this study are to investigate the presence and localization of NIS expression in pure testicular seminomas, lymph nodes with seminoma metastasis, and embryonal carcinomas by immunohistochemical methods and to discuss RAI treatment as an alternative therapy.

This study was presented at the 25th National Congress on Pathology, 14-17 October 2015, Bursa, Turkey.

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MATERIALS and METHODS

Patients

The study materials were 37 pure seminomas, two lymph nodes with seminoma metastasis, and two embryonal carcinomas from the patients who had radical orchiectomy and/or lymph node dissection between 2006 and 2011. Approval was obtained from the ethics committee of our hospital before the study. Informed consent was implied because of the retrospective design of this study.

Immunohistochemical Studies and Grading

Whole sections of the formalin-fixed paraffin-embedded tissues of the cases were stained by the avidin-biotin peroxidase complex method using anti-NIS antibody [SPM186] (Abcam, Cambridge, USA; dilution 1:100) by automatized staining system (Leica, Weitzlar, Germany). Hyperplastic thyroid tissue was used as a positive control. Sections of formalin-fixed paraffin-embedded tissues 4 μm in thickness were fixed on slides covered with poly-L-lysine. After one-night incubation at 37-40°C, dewaxing of the 4 μm sections was completed by another 45 minutes of incubation at 65°C and immersion in xylol for 20 minutes. Slides were rehydrated in alcohol and hydrated in distilled water. For regaining the antigen, the slides were boiled in water buffered with ethylenediaminetetraacetic acid (EDTA; pH: 9.0; Leica, Weitzlar, Germany) and buffer/citrate (pH: 6.0) at 95-99°C for 10 minutes. After the slides were cooled at room temperature for 15-20 minutes, washed with distilled water, and applied with 3% hydrogen peroxide at room temperature for 15 minutes for blocking endogenous peroxidase activity, they were then immerged into distilled water. After washing with phosphate-buffered saline (PBS; 0.01 M), Superblock was applied to the sections and waited for 3-5 minutes. Then the primer antibody was dripped and waited for 30-45 minutes. After washing with PBS, the slides were incubated with a biotin-antibody complex at room temperature for 20 minutes and washed again with PBS for 5 minutes. Slides were incubated at room temperature for 10 minutes with conjugate streptavidin enzyme and washed with PBS. Then 3.3'-diaminobenzidine (Leica, Weitzlar, Germany) chromogen was applied and washed with distilled water. The slides were counterstained with Harris hematoxylin for 10 seconds, then washed with distilled water and dried in alcohol. The slides were mounted with balsam before being examined.

Sodium ioidide symporter expression was evaluated immunohistochemically from whole surface sections of 34 out of 37 pure testicular seminomas that had paraffin-embedded blocks, two lymph nodes with seminoma metastasis, and a separate group of two embryonal carcinomas. Localization of NIS expression was scored as positive according to >10% cytoplasmic membranous staining and no cytoplasmic membranous staining, respectively. Purely cytoplasmic staining was noted as present or absent. Measured diameters of the tumors were recorded in centimeters during macroscopic examination. The presence of multifocal tumors was noted. After verification of the diagnosis of the cases by examining the hematoxylin-eosin stained sections with a light microscope, hilar tissue, tunica vaginalis, lymphovascular tissues, rete testis, and epididymis were reexamined for the invasions. The invasions were compared to NIS expression. The computerized tomography scans and serum markers of 29 follow-up cases (17-101 months) were used for clinical relapse diagnosis.

Statistical Analysis

The Statistical Package for Social Sciences version 18.0 (IBM Corp.; Armonk, NY, USA) program carried out the statistical analysis of the results. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The mean age of the patients was (34.4±7.4). The tumors were mostly unifocal (89.2%, 33/37). Rete testis invasion was detected in 28.2% (11/37) of the cases while epididymis invasion was found only in 10.1% (4/37). Lymphovascular invasion was seen in 64.1% (25/37) of the tumors. Relapse was seen in three out of 29 follow-up patients. There was no membranous staining in pure seminomas. Both membranous and cytoplasmic staining were not observed in two lymph nodes with seminoma metastasis. Membranous expression was present in two embryonal carcinomas (Figure 1). Cytoplasmic staining was present in 41%

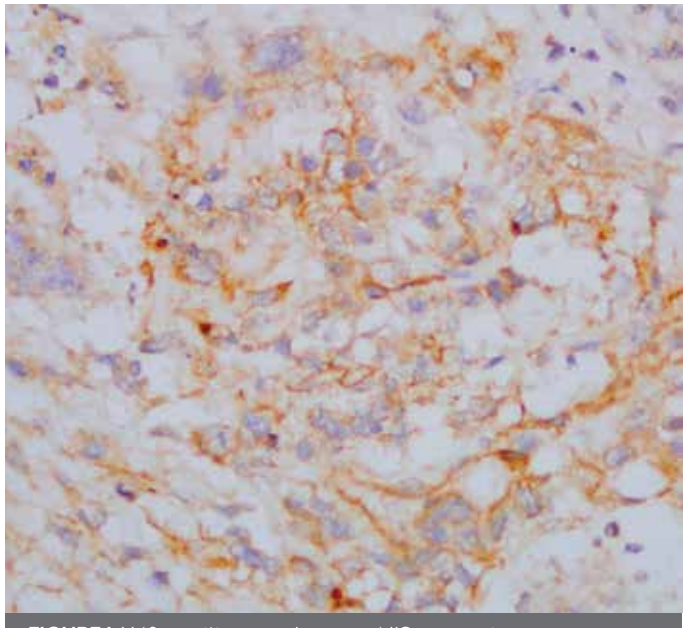

FIGURE 1. X40; positive membranous NIS expression
NIS: sodium ioidide symporter

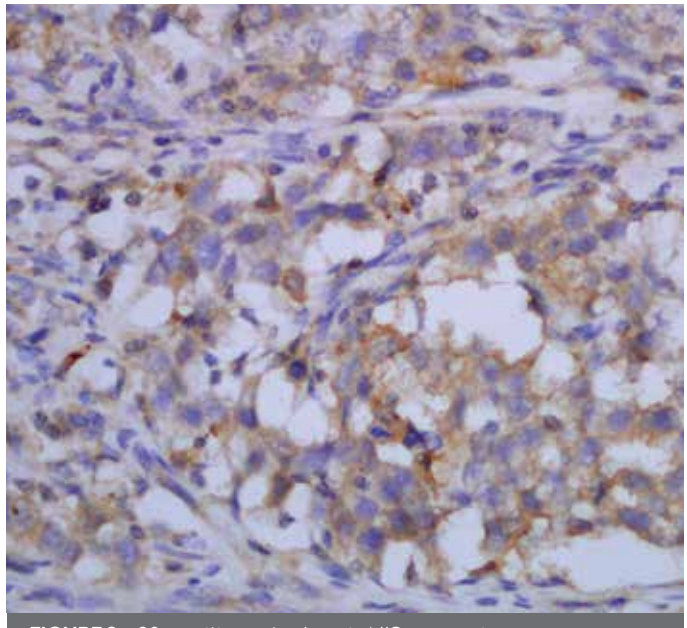

FIGURE 2. x20; positive cytoplasmic NIS expression
NIS: sodium ioidide symporter

TABLE I. NIS expression in testicular seminomas and the correlation of clinic-pathological parameters

	Cytoplasmic NIS Expression		
	Positive Number (%)	Negative Number (%)	p
Age (mean±SD)	37.13±8.14	32±7.27	0.94
Lymphovascular invasion			
Present	11 (50.0)	5 (50.0)	>0.005
Absent	11 (50.0)	5 (50.0)	
Rete testis invasion			
Present	8 (72.7)	3 (27.3)	0.135
Absent	8 (38.1)	13 (61.9)	
Epididymis invasion			
Present	3 (75)	1 (25)	0.6
Absent	13 (46.4)	15 (53.6)	

NIS: sodium ioidide symporter

(16/34) of the tumors (Figure 2). The mean ages of the patients with tumors with and without cytoplasmic staining were 37.1±8.1 and 32±7.3, respectively, (p=0.094). Rete testis and epididymis invasions were present in 72.7% and 75% of the cases with cytoplasmic NIS expression, respectively (p=0.135 and p=0.6). There was no statistically important relationship with the cytoplasmic expression of NIS, lymphovascular invasion, and the other parameters (p>0.05) (Table I).

DISCUSSION

In our study, cytoplasmic NIS expression was observed in pure seminomas. There was neither membranous nor cytoplasmic NIS expression in two retroperitoneal lymph nodes with metastasis. Membranous expression was determined in two embryonal carcinomas.

However, Micali et al. (5) observed >50% high intensity of membranous staining in 64 seminomas and five embryonal carcinomas. Usage of different clones of the monoclonal NIS antibody may be the reason of the different results, as a similar method was used in our study as in Micali et al. (5). Evaluations with NIS antibodies of different clones in a larger series of testis tumors will provide the opportunity for comparison. The investigation of NIS mRNA and protein levels by other methods like western blotting or polymerase chain reaction will be helpful to understand the difference.

Micali et al. (5) determined NIS mRNA expression in five out of eight seminoma cases, but in one of the positive cases, NIS staining was weak with the immunohistochemical method. Micali et al. (5) did not include lymph nodes in their research. There is a need for more studies about metastatic lymph nodes.

In our study, cytoplasmic staining of NIS expression was determined more in rete testis and epididymis invasions. The meaning of cytoplasmic expression is still unclear. The results of Peyrotties et al. (9) show that the intracellular expression of NIS relates to a non-specific signal. Rete testis invasion is thought to be a marker of aggressive behavior of testis tumors (10). Tumor size and rete testis invasion were additional important factors to guide treatment of malignant germ cell testis tumors (11). On the other hand, contrary to our study, Micali et al. (5) found a relationship between membranous expression and lymphovascular invasion. More prospective studies should be done about these parameters for prognostic information.

Standard treatments of seminomas are radical orchiectomy, paraaortic and pelvic lymph node dissection, adjuvant radiotherapy, and chemotherapy. Although seminomas are usually early-stage tumors and curable with standard treatments, chemotherapy after surgery is preferred for non-seminomatous tumors. Güden et al. (12) reported that five-year survival and five-year disease-free survival rates were 98.6% and 90.54%, respectively, in 74 stage I seminomas. According to the World Health Organization toxicity scale, grade I and II enteritis were reported as 9.4% and 5.4% while grade I and II nausea and vomiting were observed in 36.4% and 5.4% of the patients, respectively (12). Radioiodine treatment is worth investigating as an alternative therapy for treatment-resistant tumors or for patients who cannot have radiotherapy or chemotherapy because of severe side effects. Radioiodine is commonly used for the ablation of the residual thyroidal tissue after surgery in thyroid cancers. Side effects like temporary dysfunction in organs like the salivary gland and testis are reported during radioiodine therapy (6).

These observations create the possibility of RAI concentration in other tissues as well. The expression of NIS protein in membranes of tissues like salivary glands, the gastric mucosa, and the lactational breast was reported in several studies (4). An intense expression of NIS was observed especially in the endometrium, urinary bladder, kidney, and bile ducts in the study by Wapnir at al. (4). The researchers also reported a weak expression in testicular tissue (4). NIS mRNA expression was found in the testis nine times less than adult thyroid tissue as determined by Russo et al. (6). NIS expression was localized in the lumen side of the seminiferous ducts and Leydig cells but not observed in Sertoli cells with immunohistochemical examination (6). Interestingly, Sodré et al. (13) reported low NIS mRNA levels in malignant thyroid nodules, and also it was expressed intracellularly. The weak expression of NIS mRNA in testicular tissue may be reason of less concentrated radioiodine. The main regulator of NIS protein is TSH in thyroidal tissue. TSH stimulates NIS transcription, and its translocation to the cell membrane and extends NIS protein half-life (3). However, TSH does not play the same role in breast tissue. The absence of a regulator factor in testicular tissue may reduce the membranous localization of NIS protein. Histone deacetylase inhibitors have shown the capacity to stimulate NIS expression in an in vitro model of Leyding cell carcinoma. This report shows the presence of epigenetic control of NIS expression in Leydig cell tumors (14). Xing and Liu demonstrated that suppressing MAP kinase and PI3/Akt pathways and histone deacetylase could stimulate NIS expression and RAI uptake in non-thyroid human cancer cells (15).

CONCLUSION

In our study, cytoplasmic NIS expression was found in nearly half of the patients with pure seminomas. Cytoplasmic NIS expression was found more in patients with rete testis or epididymis invasion. The clinical importance of cytoplasmic NIS expression in pure seminomas is not clear. More researches about NIS

expression with larger series in pure seminomas and other germ cell tumors are needed to clear the option of RAI treatment.

Also, the finding of evidence about different expression profiles in non-seminomatous testicular tumors should be investigated.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Atatürk Training and Research Hospital (Decision No: 10715/2015-166).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Review

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Cancer in North Cyprus: I. Current Status, An Overview

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This is the first of a two-part review dealing with cancer issues in North Cyprus (NC). Here we give an account of what is known about the cancer status of the island, which has been debated quite intensely over the years. From several independent reports, it is concluded that the epidemiology of cancer in NC has been steady around 200-230 per 100,000 for more than 20 years. This level is in line with the rest of Europe. Nevertheless, there are some potentially worrying signs. First, the "age-standardized rate" of some cancers (lung, skin, and liver) appears higher. Second, the "average age of incidence" is lower for breast and skin cancer in NC than in the rest of Europe. Relevant environmental factors of current interest that could contribute to these issues include the environmental levels of potentially carcinogenic heavy metals (e.g., arsenic, cadmium and lead) and the levels of vitamin D in the population. The particular case of the copper mines in the Lefke region is also covered. We conclude that (i) the overall cancer status of NC is broadly comparable to the rest of Europe, (ii) continuous monitoring of epidemiology is necessary, and (iii) research is needed into the possible cause(s) of cancer, especially environmental factors.

Keywords: Cancer, North Cyprus, epidemiology, heavy metal, vitamin D

INTRODUCTION

Cancer is now very much a part of modern life, its incidence increasing in line with life expectancy. At present, one in three men and one in three women in the Western world are expected to be diagnosed with some form of cancer during his/her lifetime (1). There were approximately 14 million new cases and 8.2 million cancer-related deaths globally in 2012 (2). According to the World Health Organization (WHO), these statistics are expected to rise by about 70% over the next two decades (3). As well as genetic disposition and age, worsening life styles (e.g., leading to obesity) and environmental impact are contributing to the problem globally. Importantly, since cancer is basically an epigenetic disease, it is malleable and can significantly be affected (promoted or suppressed) by external factors, especially environment, diet and lifestyle. Accordingly, cancers of the world can be divided into two groups. On the one hand, "cancers of affluence" (e.g., melanoma and cancers of thyroid and testis) are associated with developed countries including the Western world. On the other hand, "cancers of poverty" (e.g., Kaposi sarcoma and cancers of the liver, larynx, cervix and penis) tend to occur in less developed countries (4). Such distinction emphasizes the potential impact of socioeconomic status (e.g., employment, education and nutrition) on several cancers. In this overview, we give an account of the cancer status in North Cyprus (NC).

EPIDEMIOLOGY

In an initial study sponsored by the Cancer Research Foundation (CRF)/Kanser Araştırma Vakfı (KAV), Hincal et al. (5) evaluated the cancer incidence in NC in comparison with countries of North Europe (NE) and South Europe (SE). The latter included several Mediterranean countries where diet and lifestyle could be expected to be closer to the conditions in NC. This study covered the period 1990-2002. Two main statistical parameters were studied: age-standardized rate (ASR) and average age of incidence (AAI). On average, there were about 110 and 120 per 100,000 cases of cancer in males and females, respectively (total=230 per 100,000). We would urge some caution in this analysis, however, since in the absence of an official cancer registry and in spite of all the efforts made by Hincal et al. to ensure data quality, the ASR values in NC may have been underestimated somehow (5). Nevertheless, the three most serious cancers in NC (for which the ASR values were higher than either one or both SE and NE) were the following: lung (males), skin (both sexes) and liver (both sexes). The incidence of the following cancers appeared better than SE and/or NE: breast, prostate, stomach (both sexes), bladder (both sexes), colorectal (female), ovary, cervix and corpus. Two points are worthy of highlighting from these analyses. First, the values of AAI for breast cancer and skin cancer were lower than both SE and NE (for both sexes in the case of skin cancer). This would be independent of any possible underestimation of ASR values and could indicate genuinely that breast and skin cancers occur at an earlier age in NC compared to the rest of Europe. Therefore, there must

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be some potential carcinogenic factor(s) in NC, most probably "external", i.e., environment and lifestyle. In the case of skin cancer, these would also include exposure to bright sunlight. Second, of the three most serious cancers, the high incidence of liver cancer was rather surprising since this is often associated with chronic hepatitis B/C viral infection and occurs most commonly in countries of the "third world" including many areas of Africa (6). Other risk factors include alcohol and arsenic (7). Nevertheless, all these three cancers are preventable.

The status of cancer in NC specifically in the year 2011 was more recently reported by Gokyigit and Demirdamar (8). The total incidence rate for all cancer cases was 201 per 100,000. This is close to the rate originally reported by Hincal et al. (5). Finally, an unofficial newspaper article reported 600 new cases of cancer in 2015 (9). Assuming the population of NC to be 300,000, this would mean 200 cases per 100,000, in line with the studies of Hincal et al. (5) and Gokyigit and Demirdamar (8). These three sets of data would indicate that the cancer incidence in NC has remained remarkably steady over the period 1990-2015. Furthermore, these rates would compare favorably with European countries where recently reported values vary in the range 224-338 per 100,000 (10). The five most common cancers reported by Gokyigit and Demirdamar (8) were breast, prostate, colorectal, thyroid, and lung. It was surprising that cancers of skin and liver were not prominent in this profile, unlike the report of Hincal et al. (5).

ENVIRONMENTAL ISSUES

Heavy Metals

Persistent heavy metal contamination in environment from both natural and anthropogenic sources can be of major concern as potential carcinogens. However, some heavy metals in the form of trace elements (e.g., selenium) at appropriate concentrations can have anticancer effects (11). Humans can be exposed to environmental heavy metals through water or by consuming vegetables and fruits that grow in contaminated soils. Plants cultivated in contaminated soil and groundwater can take up heavy metals through their roots and accumulate them in their edible parts. Analyses of heavy metals in soil and water of NC have been undertaken in continuing studies by CRF/KAV.

An initial partnership between CRF/KAV and Frederick Institute of Technology (FIT) in South Cyprus (SC), beginning in 2003, focused on selenium and covered different areas of Cyprus selected according to agricultural usage. A total of 481 composite soil samples were collected (225 samples from NC and 256 samples from SC) and analyzed in two independent laboratories. The average levels of selenium in the rainy season ranged between 0.00 and 0.26 ppm in NC and between 0.00 and 0.18 ppm in SC. On the other hand, in the dry season, the upper limits were observed to increase up to 0.41 ppm in NC and 0.44 ppm in SC. Taking 0.2 ppm as the optimum for deriving health benefits (e.g., by enhancing the immune system), as recommended by the U.S. Environmental Protection Agency (EPA), these areas can be accepted as fit for agriculture (12).

In 2005, the collaboration between CRF/KAV and FIT was extended to analyses of lead, cadmium, and arsenic in 260 composite soil samples (140 from NC and 120 from SC), covering Güzelyurt, Bostancı, Yuvacık, Lefkoşa, Karpaz, Alevkayası, Kırnı, and Mesarya in NC and Dhali, Sotira, Omodos, Acheilia, Polis, and Evrychu in SC (13). The results were as follows:

I. Lead: The level was in the range 5.7-224.9 ppm in NC and 4.7-121.7 ppm in SC. Since the maximum allowable limit of lead in soil has been determined to be 400 ppm by the EPA, all areas in Cyprus seem to be safe with no risk to agriculture. However, we should stress that the concentrations of lead in soils taken from NC are noticeably higher than those taken from SC.

2. Cadmium: The cadmium levels found to range between 0.2 and 1.89 ppm in NC and 0.2 and 0.59 ppm in SC, with the highest value in Nicosia (1.89 ppm). These concentrations are partially above the maximum (1 ppm) level recommended by the EPA.

3. Arsenic: High levels of this heavy metal were found over the whole island. The arsenic concentrations ranged between 0.2 and 18.5 ppm in NC and 2.8 and 22.5 in SC, compared with the maximum safe limit of only 10 ppm. At present, the relative contributions of natural versus anthropogenic sources to these high levels are not known. Further work is required to determine the relative contributions of such sources and whether arsenic enters the food chain at any stage. Importantly, it would be possible to regulate environmental arsenic levels through specialized vegetation and/or using graphene (14, 15).

THE CASE OF THE COPPER MINES

The copper mines in the Lefke region of NC were exploited by Phoenicians and Romans over 2000 years ago. The deposits were re-activated around 1920 and this continued until 1974. Afterward, the entire site was made idle with only periodic plans for reclamation. Currently, there are approximately 10 million tons of contaminated tailings including potential carcinogenic heavy metals (16). It has been officially reported that the economic value of the tailings can cover around only half of the cost for reclamation (17). The major tailings pond, which will also be the major location for burying contaminated tailings, was constructed near the Gemikonağı artificial pond. Beneath this, a geomembrane was laid to stop seepage to underground water resources. Having underground wells providing potable water could increase the risk of contamination of the drinking water resources in the Lefke area. Consequently, new locations with improved geomembrane systems may be necessary. In fact, these tailings may not threaten just the Lefke region but could affect the entire island, even extending into the Mediterranean at large. Also, apart from copper, the tailings include the following chemicals: sodium cyanide, sulfuric acid, sodium sulfide, potassium ethyl/amyl xanthane, sodium ethyl/isopropyl xanthane, carbon disulfate, pine oil, and trichloroethylene (16). These additional chemicals originate from their use during the historic ore-processing methods to extract copper and gold (16).

Whether the defunct mines are a cause of cancer has been debated for a long time, without a clear conclusion. Interestingly, in the recent study of Gokyigit and Demirdamar (8), the highest cancer rate was found in the Güzelyurt-Lefke area. More generally, although copper is a micronutrient essential for normal life, with dozens of enzymes depending on it for their regular functioning, cancer cells can utilize the metal to promote their growth (18). In one study, drinking water containing 20 μM cop-

per (the maximum level allowed in municipal drinking water according to the EPA standards) did not induce any cancer but it did promote existing tumors (19). Also, interestingly, a copper-chelating drug, tetrathiomolybdate, was recently found to produce remarkable beneficial effects against breast cancer, including metastatic disease and recurrence, in humans and mice (20). Taken together, the available evidence would suggest that copper levels in the Lefke region should be monitored both in the environment (soil and water) and in the human body. The epidemiology of the region should also be monitored.

VITAMIN D

As already emphasized, cancer involves interactions between genes and "external" factors, especially environment and lifestyle. Balanced diet is essential for healthy living. Links between nutrition and cancer were highlighted many years ago and it was estimated that more than one third of all cancers might be attributable to dietary factors (21).

Vitamin D, a fat-soluble micronutrient, is an essential precursor to the steroid hormone calcitriol, the main physiological role of which is regulation of calcium and inorganic phosphate homeostasis for skeletal health (22). In humans, vitamin D is obtained mainly through synthesis in skin by exposure to sunlight and, to a lesser extent, by directly ingestion in certain foods or supplements. Unfortified foods that contain vitamin D naturally are limited mainly to oily fish, liver, and egg yolks (23). Even with optimal nutrition, however, up to 90% of our daily vitamin D requirement is met through cutaneous production driven by exposure to sunlight (24).

A negative association between vitamin D and colon cancer risk was noted originally by Garland and Garland (25). This has now been confirmed for many other cancers, including breast, prostate, and pancreatic cancers (26, 27). Many preclinical, epidemiological and clinical studies have been performed to understand the mechanism through which vitamin D may reduce cancer risk (28, 29). The primary mode of action of vitamin D is genomic whereby binding of 1.25(OH)2D3, the major metabolite of vitamin D, to the nuclear "vitamin D receptor", a transcription factor, leads to regulation of hundreds of genes in a cell-specific fashion. Net effects include strong suppression of cancer cell proliferation and differentiation (30). More recent evidence suggests, however, that vitamin D can also exert fast, non-genomic actions (31, 32).

An important advantage of vitamin D is that, unlike some supplements, its positive effects can occur even during cancer treatment without any apparent clash. This has been seen in a patient undergoing chemotherapy or biphosphonate treatment including reduction of some of the undesirable side effects of the treatments (33).

There has not been any systematic study of vitamin D levels in cancer patients (or healthy individuals) in NC. However, anecdotal evidence would suggest that the levels in cancer patients are often low (M.B.A. Djamgoz, unpublished observations). Interestingly, more than 80% of the Saudi Arabian population suffers from vitamin D deficiency (34). It would seem, therefore, that the input (sunlight) being available in plentiful is no guarantee that healthy levels of bodily vitamin D will be attained. If so, it is possible that the metabolic pathway responsible for synthesizing vitamin D does not function normally in cancer patients or even in some healthy people (29, 35). Such abnormality may include polymorphisms in the vitamin D receptor (36).

CONCLUSION

In conclusion, although cancer incidence in NC is broadly in line with the rest of Europe, there are some negative signs that should be taken seriously. We would recommend that there should be continuous cancer awareness programs (targeting the population of all ages) and monitor of cancer cases. Research is also necessary to determine the cause(s) of those cancers for which ASR and/or AII values appear relatively worse compared with SE and/or NE.

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Review

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Cancer in North Cyprus: 2. Biomedical Research Activities

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This is the second part of a two-part review on the cancer status of North Cyprus. Here, we give an overview of the various areas of research on cancer. There are four main areas of ongoing biomedical investigation. First, monitoring of possible carcinogenic chemical factors in the environment (soil and water) is focused on arsenic. Arsenic has been found to exist broadly over the island at levels above the minimum level advised by the Environmental Protection Agency. At present, the source(s) of environmental arsenic is unclear. Second, pathophysiological mechanisms of breast and prostate cancer are being investigated with a focus on ion channels (particularly, the voltage-gated sodium channel) driving the metastatic process. In particular, the triangular relationship involving the channel, its persistent current component, and tumor hypoxia is being elucidated. Third, a further emerging theme is the association of microbiota with cancer. The possible roles of bacterial infections or microbiota in preventing, treating, or causing several types of cancers are among these projects. Fourth, a range of developments in nanotechnology is being considered. It is concluded that the island offers significant opportunities for internationally competitive, multi-faceted research on cancer.

Keywords: Cancer research, North Cyprus, environment, ion channel, microbiology

INTRODUCTION

Our understanding of cancer processes has increased steadily in the last 20 years, the "post-genomic era". Cancer is primarily an epigenetic disease caused by external factors including environmental carcinogens, diet, and lifestyle. The main cause of death in most cancer cases is metastasis, the process in which tumor cells escape from the primary site, enter the circulation (blood and/or lymph) and spread to distant organs where they lodge and re-proliferate to form secondary tumors. This is responsible for approximately 90% of deaths from cancer. Treatment of metastatic disease is invariably systemic (e.g., employing chemotherapy) and suffers frequently from undesirable side effects, including collateral damage to healthy tissues and limited duration of effectiveness, resulting from multi-drug resistance. Hence, identification of novel biomarkers; targets; and early, definitive, and functional diagnosis is necessary to increase the chance of survival.

Previously, we reviewed the cancer status in North Cyprus (NC) (1). It was concluded that whilst cancer incidence in NC is broadly comparable to the rest of Europe, there are some signs of concern. In particular, the incidence of lung, skin, and liver cancers appeared higher and the average age of incidence was lower for breast and skin cancers in NC compared with the rest of Europe. This raised the possibility that "external" factors could be promoting some cancers. It was suggested that continuous monitoring of the environment and research were necessary to understand the possible cause(s) of cancer on the island.

In this part 2 of the overview, we give an account of the cancer-associated biomedical research being conducted in NC, especially at the Biotechnology Research Centre (BRC) of the Cyprus International University. This research is multi-faceted and both "pure" and "applied" in nature, encompassing four main areas.

Environmental Studies

These are centered on arsenic (As), extending the initial joint studies of Cancer Research Foundation/Kanser Araştırma Vakfı (CRF/KAV) and the Frederick Institute of Technology (FIT). Arsenic is a naturally occurring metalloid, classified as a "Group I" human poison and carcinogen by the International Agency Research on Cancer (IARC). Arsenic present in the environment can reach humans via drinking water, agricultural products/food, dermal contact and inhalation of dust. Chronic As poisoning can lead to a variety of adverse health effects including cancers of skin, lung and bladder in addition to cardiovascular diseases, diabetes and gastrointestinal disorders (2). There are two main sources of environmental As: natural (representing the indigenous geological make-up) and anthropogenic (e.g., mining, agriculture and industrial ac-

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tivities). Drinking groundwater containing even naturally occurring high levels of inorganic As can cause large-scale poisoning. Also, plants grown in contaminated areas can transmit As (and other potential carcinogenic metals) via their roots to aerial parts such as stem, leaves and fruits. It has been shown that tuberous vegetables, such as radish, potato and carrot accumulate higher levels of As compared with leafy vegetables such as spinach, amaranthus, cabbage and even less As is accumulated by fruity vegetables such as tomato, eggplant, cauliflower, and bitter gourd. This is followed by pulses such as lentil and pea (3). Biswas et al. (4), on the other hand, reported significantly higher concentration of As in lentil, pea and spinach compared to all tuberous vegetable types. Such contrasting reports would imply that the dynamics of As absorption (and storage) from soil by vegetation is complex and requires further investigation.

We are extending studies on As, following from the initial findings that potentially high As levels are present on the island (5). Preliminary studies have been conducted on soil and water samples collected from Hisarköy, Esentepe, Beyarmudu, Akdoğan and Kalavaç. Within the scope of these pilot studies, As has been detected in some water samples, suggesting strongly the necessity to continue and extend the analyses.

More generally, recent evidence suggests that incidence of As poisoning from groundwater is rising in some parts of the world (6). Because almost 80% of agriculture in NC is carried out in the Guzelyurt region and these agricultural products are consumed all around the island, a new project has been established focusing on this region. The project, funded by EU, is currently under planning at the BRC and will be conducted within the scope of a PhD project. The first aim of this project is to determine As levels in agricultural soil, irrigation water and plants grown in nine selected villages in the Guzelyurt area. The second aim is to evaluate the possible transmission of As to humans. For this, simple body parts (hair, nail clippings and urine samples) will be collected from residents and tested. Thus, the effect, if any, of various environmental parameters (e.g., pH) on possible transmission of As from soil/water to humans will be assessed systematically.

A further project investigates possible As contamination of milk. Milk is a common part of primary nutrition, essential for child growth and body maintenance. It is also thought to protect adults against infectious and non-communicable diseases. Milk has been proposed to be a "complete food", because it contains crucial supplements including proteins, essential fatty acids, lactose, vitamins, and minerals in balanced proportion. However, milk and dairy products can also accumulate contaminants (including As) and chemical hazards (7). The fatty nature of milk is also an ideal medium for dissolving lipophilic compounds such as pesticides and certain hormones (8). Within the scope of this project, monitoring of milk samples from several villages in the Mesaria region, where dairy farming is intensive, is ongoing.

Pathophysiological Mechanisms of Cancer: Role of Ion Channels

This project builds on the discovery of voltage-gated sodium channel (VGSC) as an accelerating mechanism in metastatic diseases (9). VGSCs are membrane-bound proteins composed of one α-subunit (VGSCα) associated with one or more axillary β-subunits (9). The VGSCα is a 200-260 kDa pore-forming protein (functionally independent of any β-subunit) and comprises four homologous domains, each with six transmembrane segments (9). Nine different VGSCα genes (Navl.l-l.9) are present in higher vertebrates. The channels are traditionally known to play a central role in regenerative electrogenesis in "excitable" cells such as neurons, skeletal muscles, cardiac myocytes, and neuroendocrine cells. More recently, VGSCs have also been found to be functionally expressed in "non-excitable" cells including astrocytes, macrophages, and human carcinoma cells. The latter include breast, prostate, colon, cervical, ovarian, non-small cell lung cancer, small cell lung cancer, lymphoma, mesothelioma, neuroblastoma, and melanoma (9, l0). Importantly, where specifically tested, the predominant VGSC isoforms found were "neonatal" splice variants: Navl.5 (breast and colon cancer) and Navl.7 (prostate cancer) (9). More recently, evidence has also been accumulating that VGSC activity promotes metastasis in animal models *in vivo* (e.g. ll). Thus, VGSCs represent a novel anti-metastatic target. In this regard, this channel offers several advantages: early, functional expression; neonatal nature (distinguishing it from other "adult" VGSCs present in the developed body); and the possibility of targeting it using non-toxic drugs.

Normally, a typical VGSC is activated by membrane depolarization and the channel becomes inactivated within a few milliseconds, thus giving rise to a transient Na^+ current (I_{NaT}). Importantly, a limited number of VGSCs may not inactivate or inactivate and re-open during prolonged depolarization. This occurs frequently under pathological conditions, especially reduced tissue oxygen level (hypoxia), and results in the development of a persistent Na^+ current (I_{NaP}). Although the amplitude of I_{NaP} is <l% that of I_{NaT}, its prolonged nature (≥l s) means high amounts of Na^+ can accumulate inside cells (l2). Such excess Na^+ can disrupt cellular homeostasis, especially the pH and Ca^{2+} regulation (l3). Hypoxic conditions develop in several types of growing solid tumors due to poor and/or altered vascular architecture (l4). Development of hypoxia is crucial to dynamic progression of primary tumorigenesis to metastasis in several human cancers.

As regards the VGSC, hypoxia has been shown to increase I_{NaP} in cardiomyocytes and in neurons (l5). In cardiomyocytes, the increased I_{NaP} and the accompanying enhanced Na^+ influx would result in slowing or reversal of Na^+-Ca^{2+} exchange and intracellular Ca^{2+} overload leading to angina (l6). A similar process has been found to occur in cancer cells and number of I_{NaP} blockers (e.g., ranolazine and riluzole) have been suggested to be potential anti-metastatic agents (l7). One of the aims of this project at BRC, supported by TUBITAK, is to study the triangular relationship involving "hypoxia-VGSC/I_{NaP}-metastatic cell behavior" and the associated signaling mechanisms. A central hypothesis is that I_{NaP} blockers, such as ranolazine, can serve as anti-metastatic drugs.

Microbiology and Cancer

There is increasing evidence that cancer and microbiology overlap significantly. On the other hand, imbalance in the composition of the natural microbiome and occurrence of certain bacterial species (e.g., *Helicobacter pylori*) have been found to promote development of cancer. On the other hand, certain microbes and microbial products can offer promise in developing novel therapeutics against cancer (l8). In particular, bacteria can exhibit preferential replication/accumulation mechanisms

inside the hypoxic micro-environment of growing tumors and can be manipulated for cancer treatment (19). The idea of using bacteria as anticancer ("immunotherapy") agents dates back to ca. 1890 when William B. Coley, a surgeon, observed that a patient with neck cancer showed recovery after developing an erysipelas infection (20).

Here, we focus on the potential utilization of bacteria and bacterial products as anticancer agents.

Human body is colonized by a wide variety of microorganisms called "microbiota", sometimes referred to as the "forgotten organ". Microbiota is composed of bacteria in a commensal, symbiotic relationship with the host. This provides various benefits when healthy and balanced, but diseases, including cancer, can arise if imbalanced. Several studies have demonstrated that "germ-free" mice or mice exposed to a heavy dose of antibiotics responded poorly to classic cancer therapies, suggesting that having a healthy gut microbiome is crucial for effective cancer treatment (21). This effect is thought to be related to the immunomodulatory function of the gut microbiota since our resident microbiome can either escalate inflammation or help tone it down. Other studies point to the direct effect of gut microbes in inducing tumors. Accordingly, immunocompromised mice with normal gut flora developed colon tumors, whereas germ-free mice did not (22). Similarly, *H. hepaticus* infection in immunocompromised mice caused colon cancer (23). Composition of microbiota also seems to play a significant role in cancer development. People with precancerous colorectal adenomas displayed excess *Fusobacterium* and *Porphyromonas* in their feces (24). These bacteria (which commonly occur in the mouth) have thus been established as predictive markers for colorectal cancer development (24). However, the "chicken or egg" question still remains: which one comes first, microbiota deregulation or cancer progression? To address this question, mice were treated with antibiotics and then a carcinogen was administered. These mice grew a smaller number of tumors compared with mice with normal microbiota (24). Furthermore, when microbiota was transferred to germ-free or antibiotic-treated mice, the tumor numbers increased upon carcinogen exposure, suggesting that the gut microbiome modulates colon tumorigenesis potentially by promoting inflammation. Conversely, feeding mice *Bifidobacteria* (found commonly in the gut) reduced melanoma progression, suggesting that presence of healthy gut microbes can reduce the burden of cancer of a distinct organ like skin (25). This bacterium is also known to stimulate body's own defenses and used is for immunotherapy. Similarly, feeding *Bacteroides fragilis* to antibiotic-treated or germ-free mice improved the animals' responses to immunotherapy probably by enhancing T-cell infiltration in tumors (24). These studies, although indicating a complex and perplexing relationship between microbiota and cancer, collectively point to the crucial relationship between a healthy immune system and a balanced gut microbiome for the prevention and treatment of cancer.

Bacterial products as oncolytic tools. Bacterial endotoxins (Lipopolysaccharides) and immune-toxins can be used for both destruction of tumor tissue and development of vaccines (26). Bacteria can also be used as vectors for gene therapy and/or administration of anticancer products (27). Spores of anaerobic bacteria can reach and germinate only in oxygen-poor tumor regions and become activated. Many anaerobic bacterial species such as *Bifidobacteria*, pathogenic *Clostridia*, and *Lactobacilli* have thus been tested for their anti-tumor effects (28). Deletion experiments on *Salmonella typhimurium* identified two genes (*msbB* and *purI*) involved in anti-cancer effects, including effects at secondary sites (28). Several other strains of bacteria such as *Listeria monocytogenes, Escherichia coli, Vibrio cholera*, and *S. cholerasuis* have also been examined as possible anticancer agents (26, 28).

Genetically engineered bacteria for gene therapy. Genetically engineered bacteria can serve as tumor-specific vectors (29). Proteins of interest can thus be expressed in a tumor microenvironment enabling powerful therapies to be applied. Such bacterial proteins include cytotoxic peptides, therapeutic proteins, and enzymes as well as diagnostic tools. For example, "tumor amplified protein expression therapy" (TAPET) using modified *S. typhimurium* has been successfully utilized as a diagnostic imaging tool (30). Also, *S. typhimurium* with mutation in the *cya/crp* gene (which would normally encode proteins regulating cyclic AMP levels) has been developed against liver cancer (31). Further, bacteria can be used to express specific host proteins to target tumors. For instance, TNF-α cloned and expressed in *C. acetobutylicum* and *B. adolescentis* showed inhibition of angiogenesis and decreased tumor growth in mouse models (32).

Prodrug therapy with bacteria. Bacterially directed enzyme prodrug therapy is another approach in which toxic side effects of bacteria can be diminished and bacteria can transform a non-toxic prodrug into a cytotoxic agent at the tumor site (33). For example, cytosine deaminase (converting 5-fluorocytosine to 5-fluorouacil) and nitroreductase (transforming CB1954 prodrug to a DNA crosslinking agent) have been utilized in *in vitro* cancer models using *Clostridium sporogenes* as a vector and have been shown to kill tumor cells (33). Similarly, another study showed that intratumoral injection of an attenuated strain of *C. novyi* reduced tumor volume in several preclinical animal models as well as in one phase I study on a human with metastatic disease (27). *Salmonella* has also been used as a vector in this case for cytosine deaminase and nitroreductase which exhibited anti-cancer effects *in vivo* (28).

Bacterial toxins as tumoricidal agents. Bacterial toxins have been tested as possible anti-cancer agents in many models and found to kill cancer cells or alter their activities related to apoptosis, proliferation and differentiation (18, 28). Cytolethal distending toxins (CDTs) and cycle inhibiting factor (CIF) inhibit mitosis, whereas bacterial "cyclomodulins" disrupt host cell metabolism (34). Cell-cycle stimulator (CNF) released by *E. coli* inhibited apoptosis and differentiation of cancer cells (35). In another phase I clinical trial, chimeric toxins, VNP20009 and TAPED-CD, have been successfully tested on cancer patients (36). Using bacterial toxins directed specifically at tumors instead of anti-cancer drugs with broader targets may reduce the side effects of traditional treatments. Furthermore, combinatorial treatments (bacteria or bacterial toxins plus anti-cancer drugs or radiotherapy) could be additionally effective in cancer treatment and be further utilized for immunotherapy.

In summary, various microbiological approaches are effective cancer treatments and can complement existing therapies.

Such approaches include live, attenuated, or dead bacteria, bacterial toxins and genetically engineered bacteria for gene and prodrug delivery as well as immunotherapy use. The symbiotic relationship between the microbiome and the human host has significant implications on various mechanisms ranging from immune regulation to metabolism. In particular, distinct imbalances in oral and gut microbiota have been implicated in various cancers including oral squamous cell carcinoma, esophageal cancer, pancreatic cancer, gall bladder cancer, and colorectal cancer (28, 36). It is important to emphasize, therefore, that a healthy lifestyle that helps maintain well-balanced microbiota can also be a crucial factor in preventing cancer. However, the functional relationship between the microbiome and cancer is complex and substantial effort will be needed to be able to clinically manipulate a patient's resident microbial communities to improve cancer prognosis. More generally, this emphasizes the importance of the microenvironment in tumor progression as well as in the immune component (37).

So far, the research carried out at BRC has focused on the interactions between bacteria (gastrointestinal and environmental species) and tumor cells. We have found that the *E. coli* strain UTI89 isolated from a patient with acute bladder infection was toxic to the strongly metastatic breast cancer MDA-MB-231 cell line (38). Interestingly, this effect depended on type I pili on bacterial cell surface, since piliated bacteria caused a significantly higher level of toxicity compared to non-piliated bacteria, and a non-pathogenic, control strain of *E. coli* (C600), grown under the same conditions (38). No such cytotoxic effect was seen on the weakly metastatic MCF-7 breast cancer cell line (39). Other research is focused on testing the possible anti-metastatic effects of various bacterial species, including *Legionella pneumophila* and its products. This bacterium, an opportunistic pathogen found in water sources and systems, also seems to have cytotoxic and anti-proliferative effects selectively on strongly metastatic cells. Further work using cellular localization/internalization, antibody blocking, and co-localization studies will help determine the mechanisms involved in such bacteria-cancer cell interactions and could lead to novel therapeutic avenues.

Nanotechnology

Nanotechnology is one of the most rapidly developing biomedical research areas worldwide. This technology generates nanometer-sized materials and facilitates molecular modelling and functionality using ultra small materials with novel properties. For example, nano-iron has super paramagnetic properties, whereas macro-iron shows only ordinary magnetic properties (40). Nanotechnology plays an important role in different unique ways and has applications in various areas of medicine, as well as biotechnology and agriculture (41).

The overall aim of nanotechnology in medicine, including cancer, is to find more efficient (faster and cheaper) solutions to clinical problems, including simultaneous diagnosis and therapy and minimization of undesirable side effects (42). Nano-drug delivery systems are also being developed as highly efficient tools for the targeted treatment of cancer (43). Such "nano-carrier" efficiency has improved the therapeutic index of drugs, for example, by improving targeting of tumors in cancer patients. Nanotechnology also reduces drug toxicity and enables the drug to achieve and maintain its therapeutic steady-state level for a longer period by increasing drug solubility and stability. Erdal et al. (44) developed bacterial polyester-based nanospheres for cancer therapy. This study showed that the synthesized nanospheres were selective for cancer cells over healthy cells, thereby enabling targeted therapy (44). In another study, the impact of protein and polymeric nanoparticles (NPs) on breast cancer was investigated (45). These experiments showed that human serum albumin (HSA) NPs were smaller in size compared with (polymer-based) PHB/CMCh nanocarriers. Cellular uptake of drug-loaded NPs was observed, and concanavalin A-coated, etoposide-loaded HAS NPs were more effective on cancer compared with normal epithelial cells and induced selective apoptotic/necrotic effects (45). Silver nanoparticles (AgNPs) have been suggested to be an attractive replacement for antibiotics due to their wider-spectrum antimicrobial activity (46). In this study, we synthesized AgNPs using leaves of *Ficus ingens*. Research also employed UV-visible, fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and Zetasizer techniques. The antimicrobial activity of the AgNPs was effective at minimum inhibitory concentrations (MICs) of 10 µg/mL for *E. coli* and 20 µg/mL for *S. typhi* and *B. cereus*. Cytotoxicity studies also indicated that the synthesized AgNPs were less toxic to normal cells than to cancerous cells, thereby indicating possible use as novel anti-cancer agents (46).

Nanotechnology is also helping to generate "smart drugs" with reduced side effects compared with conventional therapies. It is expected that nanotechnology will assist in the building of molecular systems with properties of living systems. Such structures could enable regeneration or replacement of body parts lost to infection, accident, or disease (47). A further development is silicon NPs with polymer-like strands holding an anti-cancer drug; these degrade upon entering the cells and discharge the contents (48). Research also aims to develop NPs to target bacteria including gold NPs irradiated with infrared light and iron oxide (FeO) NPs coated with polymer (49).

Another study performed in our laboratory showed that pathogens can be detected using NPs coated with polymeric materials such as chitosan and carboxymethyl chitosan. However, increasing the amount of cross-linker reduced NP production due to formation of denser particles. It would appear, therefore, that cross linking can optimize stabilization of NPs, reducing degradation and increasing surface/volume ratio, thus increasing the capacity of capturing pathogens. Appropriate surface coating with polymeric materials can enable direct immobilization of associated bio-recognition groups on the surface of NPs. The type of functional groups used is an important factor that can affect the stability of magnetic NPs. Thus, this investigation showed that magnetic NPs have a great potential and promising future for pathogen detection. It may ultimately also be possible to modify these NPs for use in cancer management. Indeed, NPs are already serving as MRI and ultrasound image contrast agents, permeation enhancers, and reporters of various types of cell behavior involved in the cancer process, such as apoptosis and angiogenesis. Other ongoing applications of nanotechnology to cancer diagnostics and therapy include the following (50):

- Carbon nanotubes: detection of DNA mutations and disease protein biomarkers;

- Dendrimers: controlled release drug delivery, image contract agents;
- Nanocrystals: improved formulation of poorly soluble drugs;
- Nanoshells: tumor-specific imaging, deep tissue thermal ablation;
- Nanowires: detection of disease protein biomarkers, DNA mutations, and gene expression;
- Quantum dots: optical detection of genes and proteins and tumor visualization.

CONCLUSION

In conclusion, research is already producing results that can throw light onto the cancer status of NC with a view to ultimately improving the relevant conditions. In particular, the levels of As (and other potential carcinogenic heavy metals) in soil, water, vegetation, and the human body need continuous monitoring. More generally, modern "awareness" programs highlighting recent positive developments, such as epigenetics, should encourage and enable people of all ages to learn what to do and what not to do whilst living with cancer in the modern world. In overall conclusion, in the achievement of these aims, the universities of the island would offer significant opportunities to the burgeoning young academic population to carry out internationally competitive multi-faceted research.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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Application of Umbilical Cord Serum in the Management of a Persistent Corneal Epithelial Defect in a Patient with Graft-versus-host Disease

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A persistent epithelial defect (PED) of the cornea is challenging in the field of ophthalmology. We present the case of a patient with a PED and its alternative management with umbilical cord serum (UCS). The patient who had the PED in both eyes was treated with UCS for 3 weeks. The epithelial defect healed, and complaints decreased at the end of treatment. UCS is an effective alternative in treating patients with PEDs.

Keywords: Persistent epithelial defect, umbilical cord serum, autologous serum, graft-versus-host disease, dry eye disease

INTRODUCTION

The management of a patient with a persistent epithelial defect (PED) of the cornea is challenging in the field of ophthalmology. It is defined as the absence of improvement in an epithelial defect within 2 weeks with conventional treatment (1). There are non-surgical and surgical options for the management of PEDs (1-7). It is essential that recently introduced alternative therapies gain popularity in the treatment of PEDs refractory to current standard therapies. Herein we presented the preparation and application of umbilical cord serum (UCS) in the management of a PED of the cornea in a patient with graft-versus-host disease.

CASE PRESENTATION

A 65-year-old female who complained of pain, tearing, and stinging in her eyes for more than 2 weeks applied to our department. The patient had undergone bone marrow transplantation 3 years before due to acute myeloid leukemia. She had graft-versus-host disease and underwent immunosuppressive therapy for 2 years. An ophthalmic examination revealed a severely dry eye, a corneal ulcer, and an epithelial defect in both eyes; she received 0.05% topical cyclosporine two times a day, a topical steroid four times a day, and artificial teardrops four times a day in both eyes (Figure 1).Photophobia, blepharospasm, and thinning of the left corneal stroma were also observed. The 0.05% topical cyclosporine A and topical steroid were discontinued. The patient was followed up only with preservative free eyedrops for two weeks instilled every hour when she was awake. Meanwhile, the corneal culture was negative. There was no improvement in her complaints and physical findings. UCS were prepared as defined by Yoon et al. (4). Umbilical cord blood was collected from patients who underwent elective cesarean section delivery whom laboratory tests were negative for hepatitis B and C and human immunodeficiency viruses at the 8th and 36th gestational week of pregnancies after obtaining informed consent. Blood samples were obtained from the umbilical vein. Each sample was kept at room temperature for clotting for approximately 2 h. Serum was isolated following centrifugation at 3000 ×g for 15 min and was diluted to a 20% concentration with balanced salt solution (BSS, Alcon Laboratories, Inc. Fort Worth, Texas 76134, USA). UCS were stored in bottles, 10 to 15 mL in volume. The patient was asked to keep the UCS bottle in a refrigerator at 4°C when used and to renew it every week and the unopened UCS bottles were kept in a freezer at -20°C. UCS was instilled 10 times a day for 2 weeks and 6 times a day at the 3rd week of treatment. In addition, artificial tears were instilled every hour when awake and moxifloxacin eyedrops were instilled four times a day for 3 weeks simultaneously with a 5-10-min interval. The corneal ulcer and epithelial defect healed in both eyes after 3 weeks of instilling UCS. Leucoma and corneal neovascularization on the left eye corneal surface were observed (Figure 2).

This study was presented at the 49th National Congress of Turkish Ophtalmology Society, 4-8 November 2015, İstanbul, Turkey.

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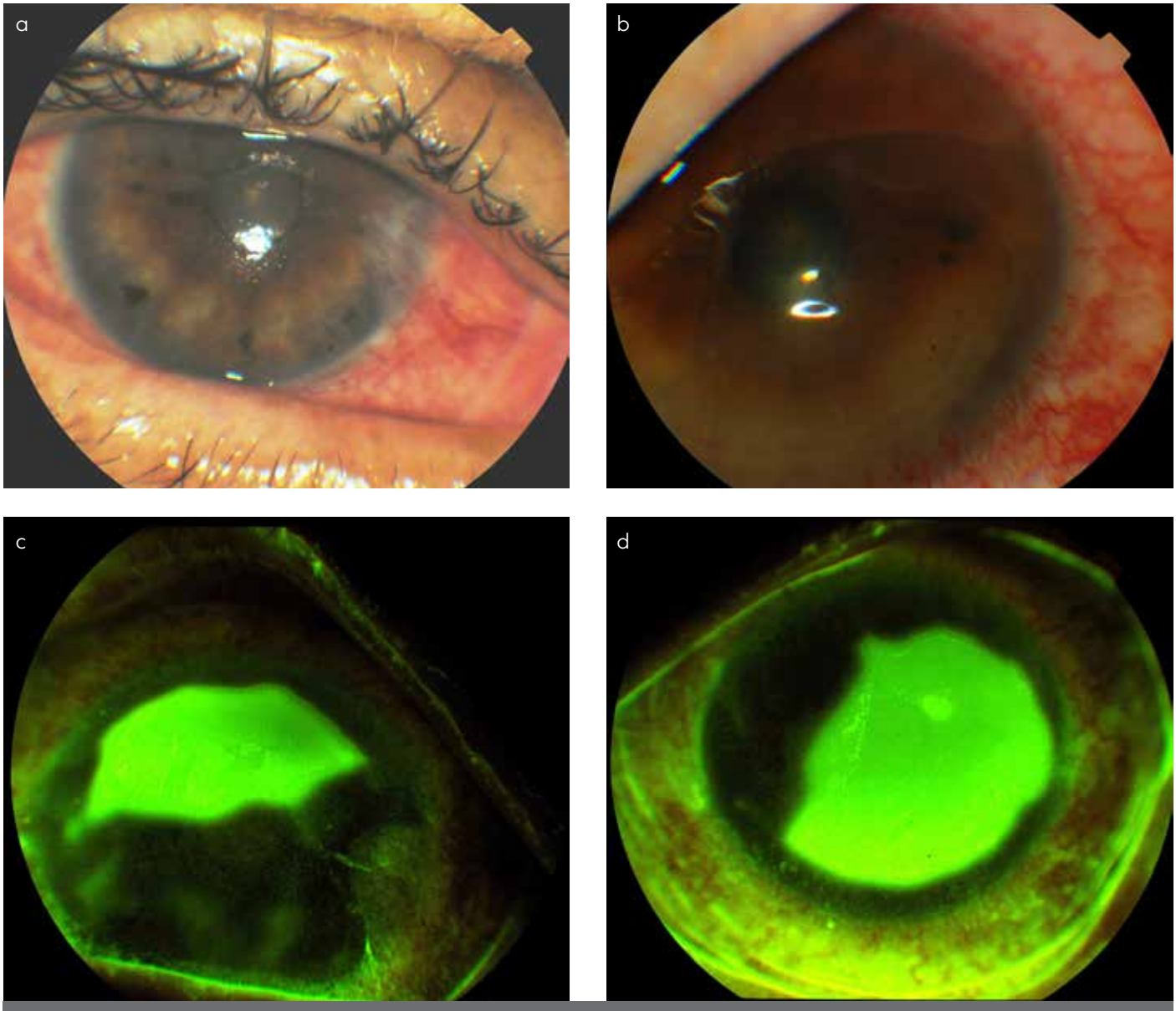

FIGURE I. a-d. Severely dry eye and epithelial defect in the right (a), and left (b) eyes. The epithelial defect and epitheliopathy stained with fluorescein in the right (c) and left (d) eyes

DISCUSSION

There are several treatment modalities for treating PEDs (2). UCS and autologous serum (AS) have been gaining popularity in recent years due to their efficacy and easy application. Both contain growth factors such as substance P, insulin-like growth factor-I, and nerve growth factor for promoting corneal epithelial migration (5). In addition, both mainly contain epidermal growth factor, vitamin A, transforming growth factor-beta, and other growth factors and neuropeptides in different concentrations that can facilitate proliferation, migration, and differentiation (4).

Some of the disadvantages in the treatment of PEDs with UCS are blood-borne infections missed in laboratory tests, infections in the window period, and contamination of UCS during preparation, transport, or storage; these might result in mild-to-serious local or systemic infections. AS might be safer than UCS in terms of blood-borne infections, but the probability of infections due to contamination using AS might be the same as that using UCS.

Umbilical cord serum is good option in patients who are not ideal candidates to receive AS such as systemically ill patients or patients with excess pro-inflammatory cytokines in serum such as graft-versus-host disease and Sjögrens syndrome (1, 6). In addition, UCS has been shown to be more effective in the healing of PEDs (7).

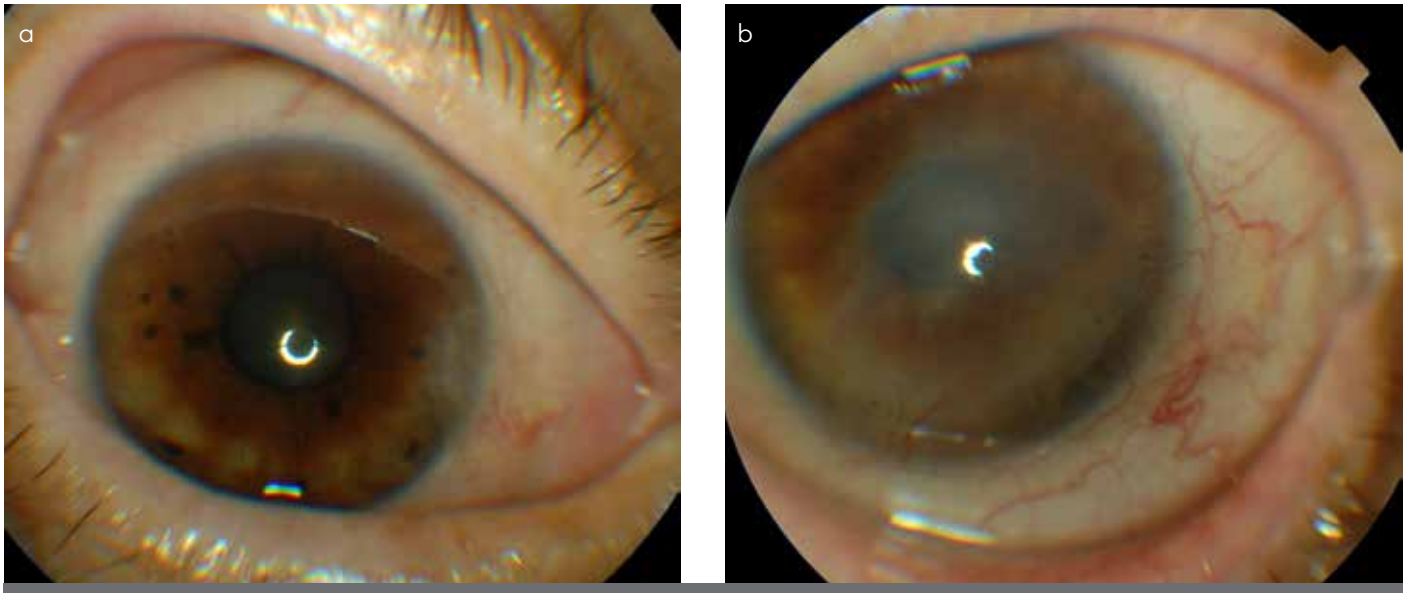

FIGURE 2. a, b. Healthy epithelium in the right eye (a), and left eye with neovascular leucoma (b) after treatment with UCS
UCS: umbilical cord serum

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.
Author contributions: Concept - E.D., B.Ö.; Design - E.D.; Supervision - E.D., B.Ö., R.E.; Resource - B.Ö.; Materials - B.Ö., E.D.; Data Collection and/or Processing - E.D., R.E.; Analysis and/or Interpretation - E.D., R.E.; Literature Search - R.E.; Writing - B.Ö.; Critical Reviews - B.Ö., E.D., R.E.

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Case Report

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A Mature Cystic Teratoma that Arises in the Posterior Mediastinum and that is Associated with an Anterior Intrathoracic Meningocele

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The frequency of a mediastinal teratoma arising in the posterior mediastinum is approximately 3%. Mediastinal teratomas are generally accidentally discovered during routine chest radiography. A 44-year-old male presented with right chest pain after falling from a height of 2 m. In this study, a rare, mature cystic teratoma that was associated with an anterior intrathoracic meningocele and that developed in the posterior mediastinum is presented. To the best of our knowledge, in Turkey, there has been no case of a posterior mediastinal teratoma associated with an anterior intrathoracic meningocele in the medical literature.

Keywords: Teratoma, posterior mediastinum, meningocele

INTRODUCTION

Nearly all benign teratomas have been observed to develop in the anterior mediastinum. The rate of teratomas that have been observed to arise in the posterior mediastinum or the ones that extend to the posterior mediastinum is only 3%. Mature teratomas are benign and slow-growing neoplasms. They usually develop within or near the thymus gland and account for up to 75% of primary germ cell tumors of the mediastinum (1). An intrathoracic meningocele is a cystic sac that has a wall formed by spinal meninges and contains cerebrospinal fluid. It protrudes into the thoracic cavity within an enlarged intervertebral foramen (2).

In this study, a rare, mature cystic teratoma that was associated with an anterior intrathoracic meningocele and that developed in the posterior mediastinum is presented. To the best of our knowledge, in Turkey, there has been no case of a posterior mediastinal teratoma associated with an anterior intrathoracic meningocele in the medical literature.

CASE PRESENTATION

A 44-year-old male presented with right chest pain after falling from a height of 2 m. A physical examination revealed no pathological findings, and his breath sounds were normal. A unilocular cystic tumor with a sharply defined contour and located in the right posterior mediastinum (Figure 1) was observed in the radiographs, computed tomography (CT) scan images, and magnetic resonance images of the chest. Besides that, a homogenous cystic mass in the left hemithorax communicating with the spinal canal through the anterior aspect of the first thoracic vertebrae was observed as a result of performing magnetic resonance imaging. The intensity of this cystic mass was similar to the cerebro-spinal fluid on T2-weighted images (Figure 2). Laboratory data were unremarkable. In addition, alpha-feto-protein and beta-human chorionic gonadotropin levels were found to be normal, and pulmonary function test results revealed a forced expiratory volume in one second (FEVI) of 2.75 (87%), a forced vital capacity (FVC) of 3.20 (81%), and an FEVI/FVC of 89%.

A posterior mediastinal mass was diagnosed, and the patient was prepared for right posterolateral thoracotomy. During this operation, a cystic mass containing brownish liquid in the posterior mediastinum was observed. The mass was in intimate contact with the esophagus and right lower pulmonary lobe. Complete excision of the mass was performed. As a result of a histopathological examination, the diagnosis of a mature cystic teratoma was confirmed and there were no other mediastinal immature or malignant tissues.

The chest catheter was removed on the third day and the patient was discharged on the fifth day after the operation. Six months later, clinical and radiological examinations were satisfactory. Written informed consent was obtained from patient who participated in this study.

This study was presented at the 9th National Congress on Thoracic Surgery, 4-7 May 2017, Antalya, Turkey.

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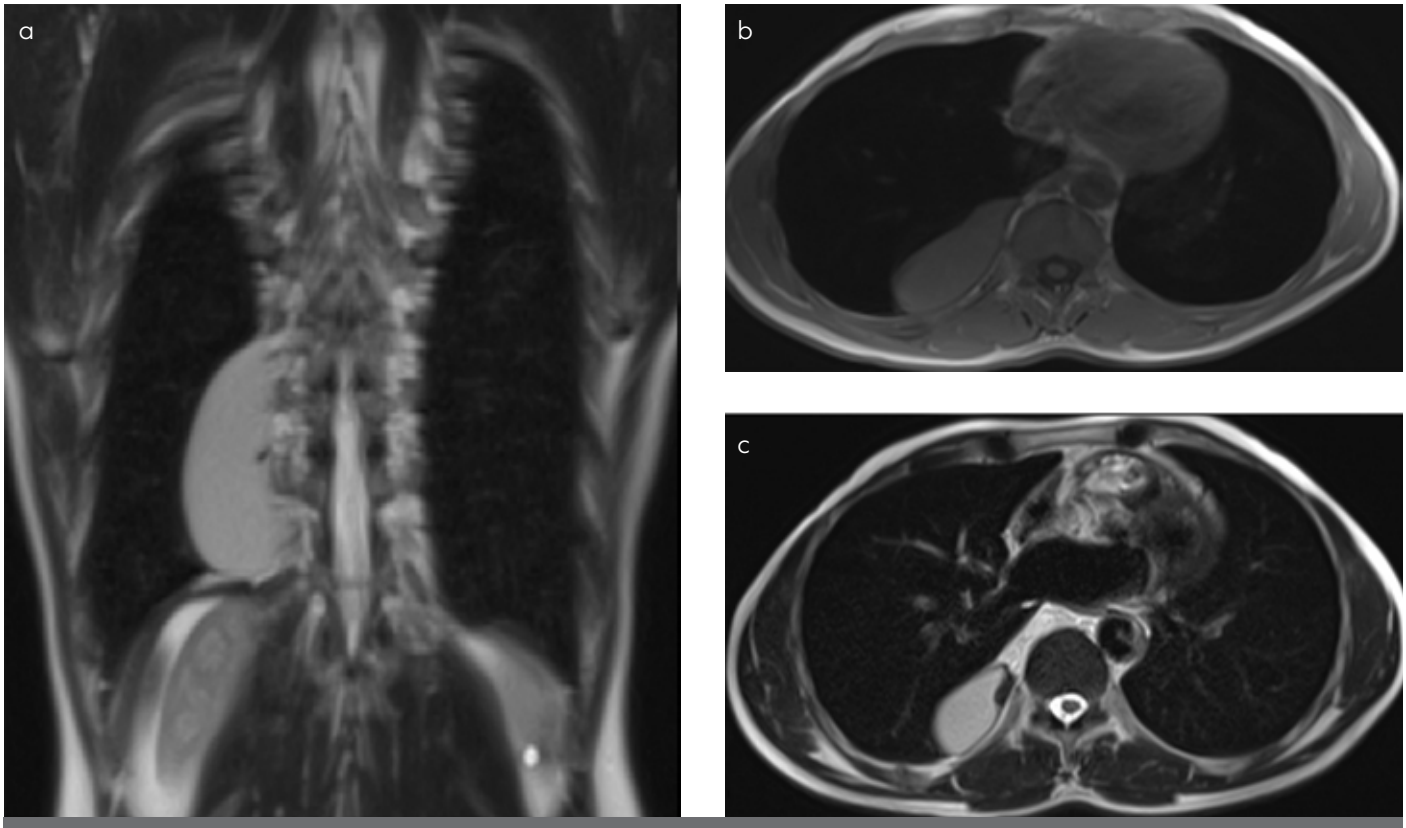

FIGURE I. a-c. Coronal (a) and axial (b, c) magnetic resonance images of the chest demonstrated a unilocular cystic tumour with a sharply defined contour located in the right posterior mediastinum

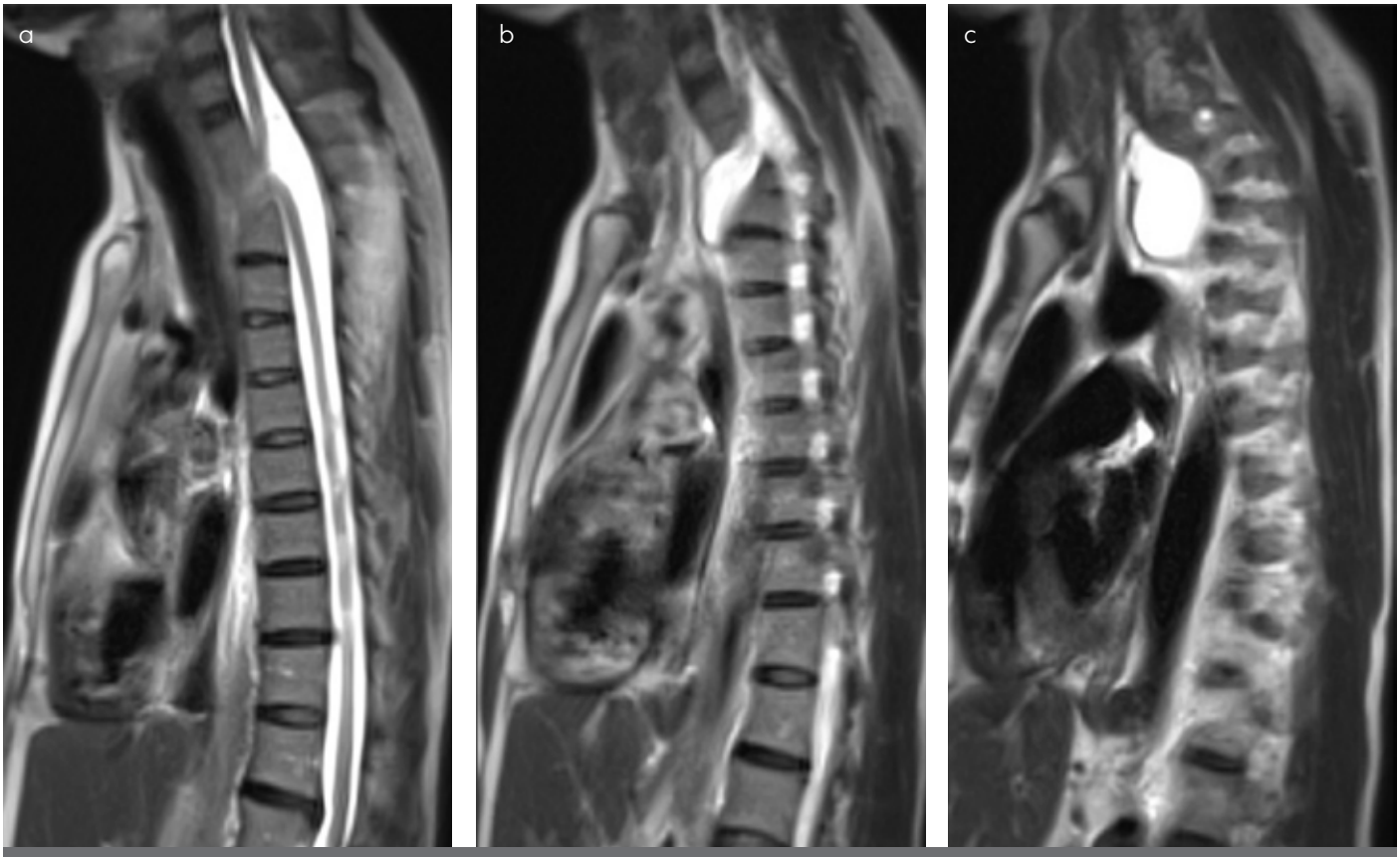

FIGURE 2. a-c. Sagital (a-c) MRI scan showed o homogenous cystic mass in left hemithorax, communicating with the spinal canal through the anterior aspect of the Ith thoraccic vertebrae

DISCUSSION

In total, 80%-90% of neurogenic tumors, paraesophageal cysts, mesenchymal tumors, and liposarcomas generally develop in the posterior mediastinum. The rate of mediastinal teratomas arising in the posterior mediastinum is only 3% (3). Mediastinal teratomas are generally accidentally diagnosed in adults during routine chest radiography. It is well circumscribed and lobulated with a large mass and with calcified areas in 20% of patients (4). In our case, the patient had fallen from a height of 2 m; he presented with right chest pain, and chest radiography revealed the posterior mediastinal lesion.

Thoracic CT is another important tool for examining teratomas because it provides the ability to clearly view the borders of the tumor along with realistic information about the structures included in the teratoma, such as soft tissues, fluids, fats, calcifications, and teeth (4, 5). There are some areas of calcification intermixed within areas of fat density of this cystic mass and it has a thick wall that can usually be diagnosed on performing a CT scan. This cystic mass should be differentiated from complicated hydatid cysts, extralobar sequestration, neurogenic tumors with necrosis, and calcified congenital cysts (1). During the CT scan of the chest in our patient, it was diagnosed in the right posterior mediastinum a unilocular cystic tumor with a sharply defined contour. During the preoperative differential diagnosis, we also included neurogenic tumors as they account for 19%-39% of mediastinal tumors and they generally develop in the posterior mediastinum (4).

The main treatment approach is total surgical excision. Posterior lateral thoracotomy is the most ideal method for this. Mature Cystic Teratomas may present difficulties if they are too close to vital neighboring structures. Takeda et al. (6) reported that after they performed complete resection, lobectomy combined with tumor extirpation was also required for three patients, additional partial resection of the lung was required for five patients, and pericardiectomy was required for seven patients. In our case, neither lung resection nor pericardial resection was required during complete resection. The recurrence rate of a teratoma is nearly zero when complete resection is performed or when it contains no immature or malignant structures (7).

An anterior spinal meningocele is rare and is generally observed in the thoracic or sacral region. Type I neurofibromatosis or Marfan syndrome and sometimes, an isolated defect frequently occur as a manifestation of generalized mesenchymal dysplasia (8). There were no neurological findings present in our patient. Presently, we have initiated conservative management and follow-up for the patient. Surgery must also be taken into consideration if any gradual increase in the size of the meningocele sac is observed during careful follow-up examinations of the patient and any neurological and/or cardiopulmonary complications are diagnosed or when an operative correction is required for a patient's kyphoscoliosis (9).

To conclude, teratomas must be considered in the differantial diagnosis of posterior mediastinal tumors. An ideal method for making such a diagnosis is the operation that may also confirm the presence of a teratoma, prevent any complications, and provide the chance of eliminating malignant components that may require adjuvant therapy.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Letter to the Editor

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Laparoscopic Management of Persistent Vitelline Artery Causing Intestinal Volvulus and Obstruction in a Child

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Dear Editor,

Persistent omphalomesenteric (vitelline) artery causing intestinal obstruction is an extremely rare congenital condition in pediatric surgery, with only a few case reports in the literature (1-3). Here we present a case that was successfully managed using a laparoscopic approach.

A 15-year-old girl presented to our Emergency Department with the complaint of sudden-onset colicky abdominal pain and bilious vomiting. The physical examination revealed tenderness and muscle guarding in the right lower quadrant. Abdominal X-ray showed dilated intestinal segments in the same area, and ultrasonography showed the same findings with free fluid in the right lower quadrant and normal appendix. We preliminarily diagnosed the condition as congenital obstructive fibrotic band compression. Emergent laparoscopic exploration was performed. A standard three-port technique was employed. During exploration, volvulated ileal loops were around an artery-like structure, which originated from the ileocecal mesentery and ended at the anterior abdominal wall, was observed by following the trace of the medial umbilical ligament (Figure 1). Volvulated loops were edematous and seemed to be obstructed. Laparoscopic devolvulation with excision of the artery and elective appendectomy was performed (Figure 2). Pathological evaluation proved the excised structure to be of arterial origin. The patient was uneventfully discharged one day after the surgery.

Persistent vitelline artery is one of the omphalomesenteric remnants, which may lead to bowel obstruction and volvulus depending on its configuration (4). The diagnosis of this condition is extremely problematic and mostly depends on the clinician's suspicion. Laparoscopic management seems to be a good option in such rare pediatric conditions.

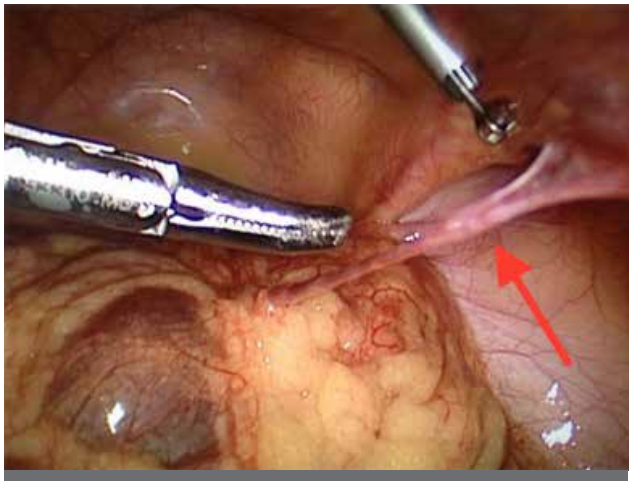

FIGURE 1. Persistent vitelline artery observed after the devolvulation procedure (red arrow)

FIGURE 2. Macroscopic view of the excised specimen

This study was presented at the 30th National Congress on Pediatric Surgery, 17-20 October 2012, Ankara, Turkey.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Letter to the Editor

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Giant Incarcerated Paraesophageal Hernia Involving the Stomach and Sigmoid Colon

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Dear Editor,

Approximately 10%-15% of the general population have hiatal hernia (HH) (1). HHs are more common in older women and are classified into four types according to the herniated organ or structure (Table 1) (2). Type II-IV hernias are usually named as paraesophageal hernias (PHs) and represent 5%-15% of all HHs (3). Giant PH has no certain definition; however, herniation of >30%-50% of the stomach is often reported as giant hernia (4).

An 88-year-old woman presented to the emergency room with a 1-week history of nausea, vomiting, constipation, and minimal abdominal distension. She also suffered from dyspnea for several months. She had no history of abdominal or thoracic surgery. On physical examination, minimal epigastric tenderness, decreased lung sounds, and tympanic bowel sounds were detected. Chest X-ray showed large air–liquid shadows superior to the central diaphragm (Figure 1). Computed tomography demonstrated a giant PH containing dilated colon and the upper part of the stomach (Figure 2). Routine blood tests were normal except increased inflammatory markers including leukocyte count (12.2×103/μL) and C-reactive protein (52.5 mg/L). At laparotomy, the upper part of the stomach and sigmoid colon were herniated into the thorax through a 4-5-cm paraesophageal defect. The migrated structures were reducted into the abdomen. There was no necrosis in the organs, and primary repair of the defect was easily performed. The patient was discharged without complications on day 7.

Most patients with PH are asymptomatic or have mild symptoms. On the other hand, as in our case, approximately one-

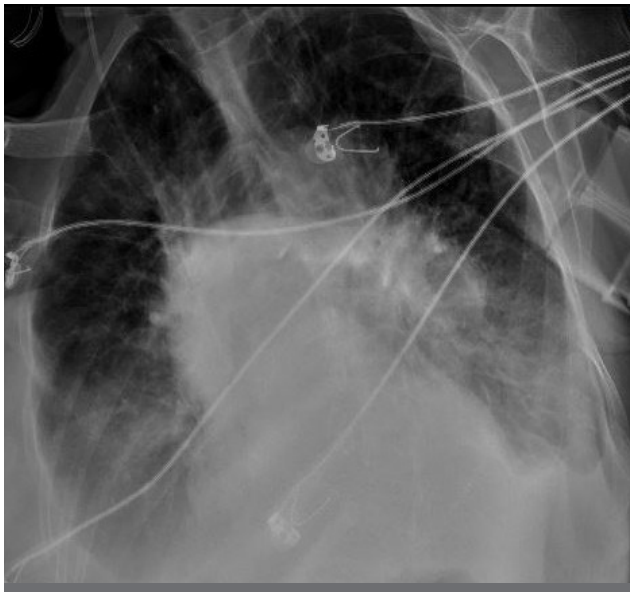

FIGURE 1. Large air–liquid shadows belong to the stomach and colon, superior to the diaphragm

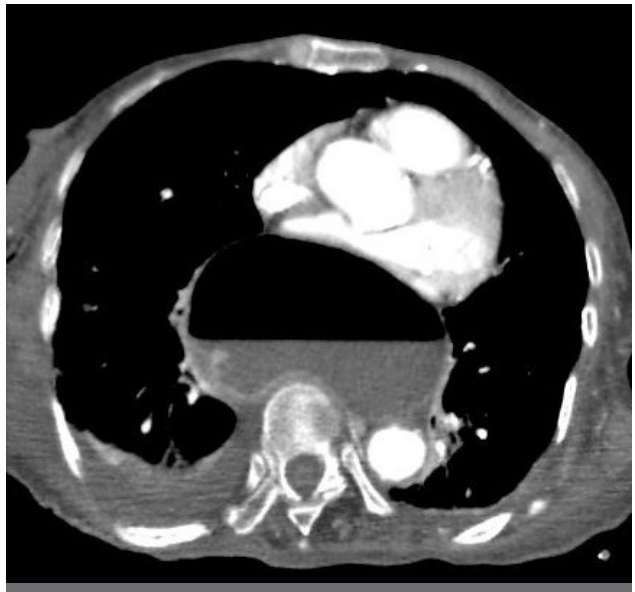

FIGURE 2. Computed tomographic image of dilated sigmoid colon and the upper part of the stomach herniated into the thorax through the paraesophageal defect

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TABLE I. Classification of Hiatal Hernias (I)

Type	Definition
Type I (Sliding hernia)	Gastroesophageal junction is herniated through the hiatus Stomach is in its normal localization.
Type II (Rolling hernia)	Fundus is herniated through the hiatus
Type III	Combination of types I and II
Type IV	Herniation of organs or structures other than the stomach

fifth of patients may present with findings of acute intestinal obstruction due to incarcerated organs, requiring emergency surgery. As a general rule, all symptomatic patients should also be surgically treated to prevent life-threatening complications including obstruction, strangulation, and perforation (1). However, poor health status can sometimes be a contraindication for surgery. Such patients can be conservatively treated, with nasogastric decompression and supportive therapy. Surgery can be performed via laparotomy or laparoscopy, and the application of synthetic material is recommended for hiatus defects of >5 cm (5). In summary, all clinicians should be aware of this dangerous condition, especially in older patients with abdominal complaints accompanying respiratory problems, and detailed physical and radiological examinations should be a part of the diagnostic workup. It should also be kept in mind that any delay in diagnosis is highly associated with life-threatening complications.

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