

Small B cell non-Hodgkin Lymphoma

## High Lights

- intramuscular injection of diclofenac sodium with negative pressure wound therapy followed by skin graft
- Use of Algorithm for the Diagnosis of Mycobacterium Tuberculosis
- Superficial Fungal Infections in Children
- Swyer syndrome after bilateral gonadectomy and adjuvant chemotherapy

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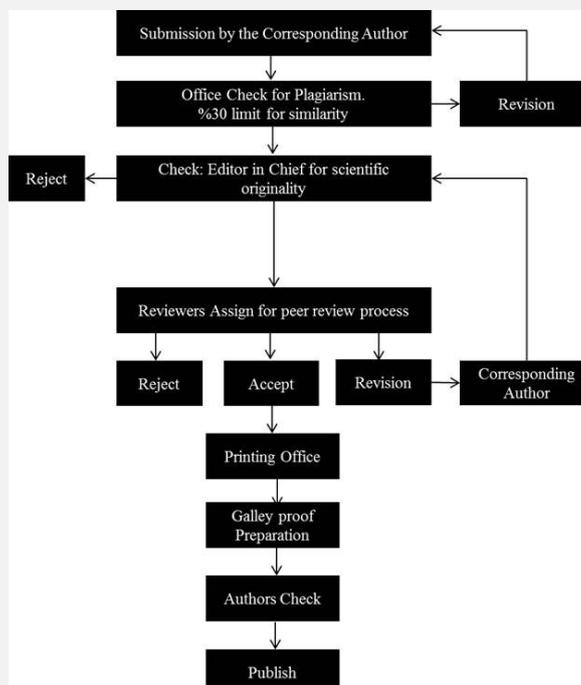
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## Reconstruction of gluteal defects related to Nicolau Syndrome secondary to intramuscular injection of diclofenac sodium with negative pressure wound therapy followed by skin graft

Omer Kokacya<sup>1\*</sup>, Ibrahim Tabakan<sup>2</sup>, Eyuphan Gencel<sup>2</sup>, Cengiz Eser<sup>2</sup>

### Abstract

**Objective:** Nicolau syndrome, synonymously livedo-like dermatitis or embolia cutis medicamentosa is a rare complication of drug injection leading to locoregional necrosis of the skin, adipose and muscular tissue. Underlying physiopathology is not well understood and there is no standart guideline for its management. However, after the demarcation of necrosis, debridement and for large wounds reconstruction is mandatory. Even though vast majority of the Nicolau syndrome cases were reported by other disciplines but the plastic surgery, there may be further need for reconstructive procedures for wound closure.

**Material and Methods:** Present study included eight patients admitted to our wound care center for necrosis at the gluteal region after intramuscular injection of diclofenac sodium who were treated with debridement, negative pressure wound therapy and skin grafts. Patients' ages, sexes, body mass indexes, underlying diseases were documented. Sizes of the lesions were measured. Injection, hospitalization, skin graft operation and discharge dates were recorded.

**Results:** All the wounds healed uneventfully but with depressed scars. Mean duration of hospitalization was 23.5 (range, 15-34) days.

**Conclusion:** In the present article, we reported that even if the hospitalization time is longer and cosmetic result is poorer, skin grafting after sufficient times of negative pressure wound therapy administration is a reliable method. We do not recommend this method as the first choice but if there is not adequate adjacent soft tissue for harvesting flaps or if a suitable perforator vessel is not found for perforator flap harvest, this reliable method should be kept in mind.

**Key Words:** Nicolau syndrome; Diclofenac, Gluteal defect; Negative pressure wound therapy; Skin graft

### Introduction

Nicolau syndrome, synonymously livedo-like dermatitis or embolia cutis medicamentosa is a rare complication of drug injection leading to locoregional necrosis of the skin, adipose and muscular tissue. It was first described by Freuhdenthal (1) in 1924 and Nicolau (2) in 1925 after intramuscular injection of bismuth salt for the treatment of syphilis.

Nicolau syndrome has been reported after injection of many other drugs such as non-steroidal anti-inflammatory drugs (3, 4), benzathine penicillin (5), buprenorphine (6), bortezomib (7), hyaluronic acid (8), oxytocin (9), glatiramer acetate (10), glucocorticoid (11), vitamin K (12), pneumococcal conjugate vaccine (13) and other vaccines (14). It may be seen following intramuscular (3-5, 9, 12), subcutaneous (7, 10, 14)

intraarticular (11), intraarterial, intravenous, failed extravascular injections (6), intradermal mesotherapy (15) and sclerotherapy (16) applications.

Even though vast majority of the Nicolau syndrome cases were reported by other disciplines but the plastic surgery, there may be further need for reconstructive procedures for wound closure.

In the present study, the authors reported eight cases of gluteal skin defects due to Nicolau syndrome secondary to intramuscular injection of diclofenac sodium, which were treated with surgical debridement, negative pressure wound therapy and skin grafts. Treatment methods are discussed.

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1 Dr. Ersin Arslan Training and Research Hospital, Dept. of Plastic Reconstructive and Aesthetic Surgery, Gaziantep, Turkey

2 Cukurova University Faculty of Medicine, Dept. of Plastic Reconstructive and Aesthetic Surgery, Adana, Turkey

\* Corresponding Author: Omer Kokacya E-mail: [kokacya@yahoo.com](mailto:kokacya@yahoo.com) Phone: +903422210700



## Material and Methods

The study included 8 patients admitted to our wound care center between April 2015 and April 2016 for necrosis at the gluteal region after intramuscular injection of diclofenac sodium who were treated with debridement, negative pressure wound therapy and skin grafts.

All patients were admitted to our clinic after demarcation of necrosis. If the demarcation of necrosis was not complete at the initial examination, the patients were followed up at outpatient clinic and they were hospitalized when the demarcations processes were complete.

For seven patients included in the study, sharp debridement was performed at the admission within the patient's bedside without need for local anesthesia and wound swab culture was obtained. In figure 1A and 1B, patient no:2 at the admission and just after sharp debridement, respectively are seen.

Then negative pressure wound therapy (Genadyne XLR8, Genadyne Biotechnologies, Great Neck, NY, USA) was administered and dressing was changed at 3 days intervals. When necessary, debridement was performed at every dressing change. One patient's (patient no:8) wound was debrided at another hospital and he was referred to our clinic for wound closure. After wound swab culture was obtained, negative pressure wound therapy was administered without need for debridement.

Wound swab cultures were repeated at every second dressing change. Patients with pathogen-positive culture results were given antibiotics chosen on the basis of the antibiogram results. Patients with pathogen-negative culture results were not given any antibiotics.

After leakage was stopped, necrotic tissues were removed and cavity was filled, split thickness skin grafts were used to cover the wounds. Operations were performed under spinal anesthesia. Patients were followed up at prone position with strict immobilization at postoperative 3days.

Patients' ages, sexes, body mass indexes underlying diseases were documented. Sizes of the lesions were measured. Injection, hospitalization, skin graft operation and discharge dates were recorded

## Results

Demographic and clinical characteristics of patients included in the study are presented in Table 1. Mean age was 63.5 (range, 48-75). Mean BMI was 34.5 (range 23-45). Mean wound size (cm<sup>2</sup>) was 109 (range, 35-270). Time intervals between injection, hospitalization, skin graft operation and discharge are presented in Table 2.



**Figure 1:** Patient no:2 A. at the admission B. just after sharp debridement

Mean time interval between injection and hospitalization was 16 (range, 7-35) days. Mean time interval between hospitalization and skin graft operation was 14 (range, 9-21) days. Mean time interval between skin graft operation and discharge was 9.4 (range, 6-13) days. Mean duration of hospitalization was 23.5 (range, 15-34) days

In Figure 2A patient no:8 at the admission is seen. Figure 2B shows the same patient after 14 days of negative pressure wound therapy and just before the skin graft operation. Figure 2C shows the same patient at postoperative 24th day of skin grafting operation

**Table 1.** Demographic and clinical characteristics of the patients

Patient no	Sex	Age	BMI	Comorbidities	Wound size (cm x cm)	Wound size (cm <sup>2</sup> )
1	Female	72	34	Essential hypertension Diabetes mellitus	8x7	56
2	Male	73	24	Monoparesis	14x15	210
3	Female	62	38		12x9	108
4	Female	54	45	Chronic osreoarthritis	6X11	66
5	Female	58	42	Diabetes mellitus	6X9	54
6	Female	48	37	Diabetes mellitus	10X7	70
7	Female	75	33	Essential hypertension	5X7	35
8	Male	66	23	Primary lung cancer	18X15	270

**Table 2.** Time intervals between injection, hospitalization, skin graft operation and discharge

Patient no	Time interval between injection and hospitalization (days)	Time interval between hospitalization and skin graft operation (days)	Time interval between skin graft operation and discharge (days)	Inpatient days
1	9	12	9	21
2	23	21	12	33
3	15	9	8	17
4	13	21	13	34
5	7	12	7	19
6	16	9	6	15
7	12	15	9	24
8	35	14	11	25

**Figure 2:** Patient no:8 A: at the admission B: after 14 days of negative pressure wound therapy and just before skin graft operation C: at the postoperative 24th day of skin graf operation

## Discussion

The actual physiopathology of Nicolau syndrome is not clear. It is presumed to be the result of direct damage, occlusion or indirect damage of an end-artery at the injection site. Most commonly hypothesized two mechanisms are direct end-artery damage with injection needle and vasospasm as a result of periarterial injection. Other one is vascular rupture due to perivascular inflammation from a cytotoxic reaction to the drug. Embolic occlusion may be the result of inadvertently intra-arterially injected drug or perivascularly injected lipophilic drugs may penetrate the blood vessels and induce occlusion(4).

Non-steroidal anti-inflammatory drugs inhibit the enzyme cyclooxygenase, preventing thus the synthesis of prostaglandin, consequently inducing vasospasm and restriction of local circulation may contribute to locoregional tissue necrosis(17). Diclofenac is one of the most commonly reported Nicolau syndrome causing drugs(18).

Regardless of the drug used and underlying physiopathology, once Nicolau syndrome developed, there is no specific conservative treatment before the demarcation of necrotic area. In most cases pain control, antibiotics and dressings may help. Steroids, anticoagulants and vasoactive agents have been emphasized for regression of livedoid lesions but tissue damage has not been reversible(19).

Ergul et.al.'s case report of a pediatrics patient claims that hyperbaric oxygen therapy with vasoactive agents started within the 24 hours of the Nicolau syndrome diagnosis can prevent the development of necrosis and tissue loss(20).

After the demarcation of the necrotic area, necrotic tissue must be debrided and one must look for the ways of closing the wound. Small defects can be closed primarily and also can be left for secondary healing or treated with negative pressure wound closure systems. Best aesthetic results are obtained by primary closure. However, larger defects may not be closed by primary closure. For the reconstruction of larger defects graft or flap should be employed. In the study of Dadaci(3) et al with 17 patients, 4 of the defects were repaired with flaps following vacuum assisted wound therapy.

Mean hospitalization duration of these 4 patients is 11,8 (range, 10-12) and is shorter than our result. In the study by Kocman Et al. 5 patients were treated with immediate debridement and free style perforator based flaps. The time interval between debridement and wound closure operation is not seen in Kocman et al.'s study and this decreases the hospitalization time. There is no doubt that cosmetic results of flap reconstruction are superior than skin grafting as skin grafting results in depressed scars.

Before the definitive surgery, administering negative pressure wound therapy after drainage and debridement ensures the closure of pockets and contributes to healing by increasing wound granulation and blood flow(3). If there is not adequate adjacent soft tissue for harvesting flaps or if a suitable perforator vessel is not found for perforator flap harvest, closing the wound with skin grafting after sufficient times of negative pressure wound therapy administration is a reliable method.

## Conclusion

Nicolau syndrome is the ischemic necrosis of skin, adipose and muscular tissue following drug injection. It can be seen after any type of injection of any kind of drugs. Underlying physiopathology is not well understood and there is no standart guideline for its management. However, after the demarcation of necrosis, debridement and for large wounds reconstruction is mandatory. In the present article, we reported that even if the hospitalization time is longer and cosmetic result is poorer, skin grafting after sufficient times of negative pressure wound therapy administration is a reliable method. We do not recommend this method as the first choice but if there is not adequate adjacent soft tissue for harvesting flaps or if a suitable perforator vessel is not found for perforator flap harvest, this reliable methos should be considered.

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical issues:** All authors declare that originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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## A Retrospective Analysis on the Use of Algorithm for the Diagnosis of Mycobacterium Tuberculosis

Huseyin Guducuoglu<sup>1\*</sup>, Abdullah Bektas<sup>2</sup>, Siddik Keskin<sup>3</sup>, Cennet Ragbetli<sup>1</sup>

### Abstract

**Objective:** The aim of this study was to investigate whether an algorithm has been used for the diagnosis of Mycobacterium tuberculosis samples over the last three years.

**Material and Methods:** A total of 1,036 samples collected between June 2010 and March 2013 were submitted to the laboratory for the diagnosis of Mycobacterium tuberculosis. The samples were studied using the Ehrlich-Ziehl-Neelsen (EZN) staining. Various culture methods such as Löwenstein-Jensen (LJ) medium-BacT/ALERT® 3D and the BD BACTEC™ MGIT™ 320 Mycobacteria Culture System were applied for 508 samples. Real-time Polymerase Chain Reaction (PCR) method was performed in 138 samples. In general, 2 or 3 samples were obtained from each patient for the diagnosis of acid-fast bacilli (AFB), whereas only one sample was obtained for culture.

**Results:** Of the EZN-positive samples, 30% were PCR-positive and 65% were culture-positive; of the culture-positive samples, 13% were PCR-positive and 54% were EZN-positive; of the PCR-positive samples, 21% were culture-positive and 43% were EZN-positive.

**Conclusion:** AFB and culture are likely to be inadequate for the determination of Mycobacterium tuberculosis. Therefore, PCR seems to be an essential need. However, the clinical table of the patient should also be considered to determine the need for PCR. Thus, an appropriate algorithm should be suggested for the diagnosis of Mycobacterium tuberculosis.

**Key words:** Mycobacterium tuberculosis, algorithm, EZN, culture, PCR

### Introduction

The classic laboratory approach to the diagnosis of mycobacterial infections involves the phenotypic characterization of colonies growing on Löwenstein-Jensen medium. The diagnostic methods used in the processing of sputum specimens in many laboratories are performed via algorithms. A combination of phenotypic and molecular assays is recommended for the rapid identification of mycobacteria, particularly for the identification of *M. tuberculosis* (1).

One of the common sputum smear microscopy is Ziehl-Neelsen, which is a fast and low-cost technique for detecting tuberculosis (TB) in high-incidence areas but has low sensitivity (2) and high specificity (3). In a study on culture, the concordance rate between the solid and liquid cultures was 92.8%.

No Mycobacterium isolates were detected in 0.4% of the cases in the liquid culture and no Mycobacterium isolates were detected in 6.8% of the cases in the solid culture (4). These results suggest that the Mycobacterium culture method exhibits high growth rates. Used as an advanced technique, PCR appears to be a promising method for the diagnosis of pulmonary tuberculosis, even in paucibacillary specimens. Simultaneous identification and faster results are additional advantages of this method (5).

Conventional bacteriological microscopy and culture are commonly used for the diagnosis of tuberculosis, particularly in developing countries. However, their limited sensitivity, specificity, and delayed results make this provision inadequate.

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1 Yüzüncü Yil University School of Medicine, Dept. of Medical Microbiology, Van

2 Mustafa Kemalpaşa Government Hospital, Dept. of Medical Microbiology, Bursa

3 Yüzüncü Yil University School of Medicine, Dept. of Biostatistics, Van

\* Corresponding Author: Huseyin Guducuoglu E-mail: [hguducuoglu@hotmail.com](mailto:hguducuoglu@hotmail.com) Phone: +904322150474/6247



Despite the development of quicker and more sensitive novel diagnostic techniques, their complexity and high cost have limited their use in many poor-resource countries. Due to the rapidly growing TB problem in these countries, there is an urgent need to assess promising alternative methodologies in settings with high disease prevalence (6).

In this study, we aimed to examine the relationships between EZN, culture and PCR and to investigate whether an algorithm has been used in the administration of these methods.

## Material and Methods

A total of 1,036 samples collected between June 2010 and March 2013 were submitted to the laboratory for the diagnosis of *Mycobacterium tuberculosis*. The samples were studied using the EZN staining. For the diagnosis of AFB, 2 or 3 samples were obtained from each patient, whereas only one sample was obtained for culture. Various culture methods including Löwenstein-Jensen (LJ) medium-BacT/ALERT® 3D and the BD BACTEC™ MGIT™ 320 *Mycobacteria* Culture System were applied for 508 samples. Real-time PCR method (Artus M. tuberculosis PCR Kits, Qiagen) was performed in 138 samples.

## Results

In this study, the evaluations were based on the results obtained from 524 EZN, 499 culture, and 138 PCR analyses. Of positive results, 11 samples were positive both on EZN and culture, 4 were positive both on EZN and PCR, 1 was positive both on culture and PCR, and 2 were positive on all tests. Of negative results, 4 samples were negative both on EZN and culture, 1 was negative both on EZN and PCR, 1 was negative both on culture and PCR, and 66 were negative on all tests (Figure 1).

In the 20 AFB-positive samples, 13 were positive on culture and 6 were positive on PCR, 5 were negative on culture and 2 were negative on PCR, and no culture and PCR analyses were request for 2 and 13 samples, respectively (Figure 2).

In the 24 culture-positive samples, 13 were positive on EZN and 3 were positive on PCR, 10 were negative on EZN and 2 were negative on PCR, and no EZN and PCR analyses were request for 1 and 19 samples, respectively (Figure 2).

In the 14 PCR-positive samples, 6 were positive on EZN and 3 were positive on culture, 6 were negative on EZN and 6 were negative on culture, and no EZN and culture analyses were request for 2 and 5 samples, respectively (Figure 2).

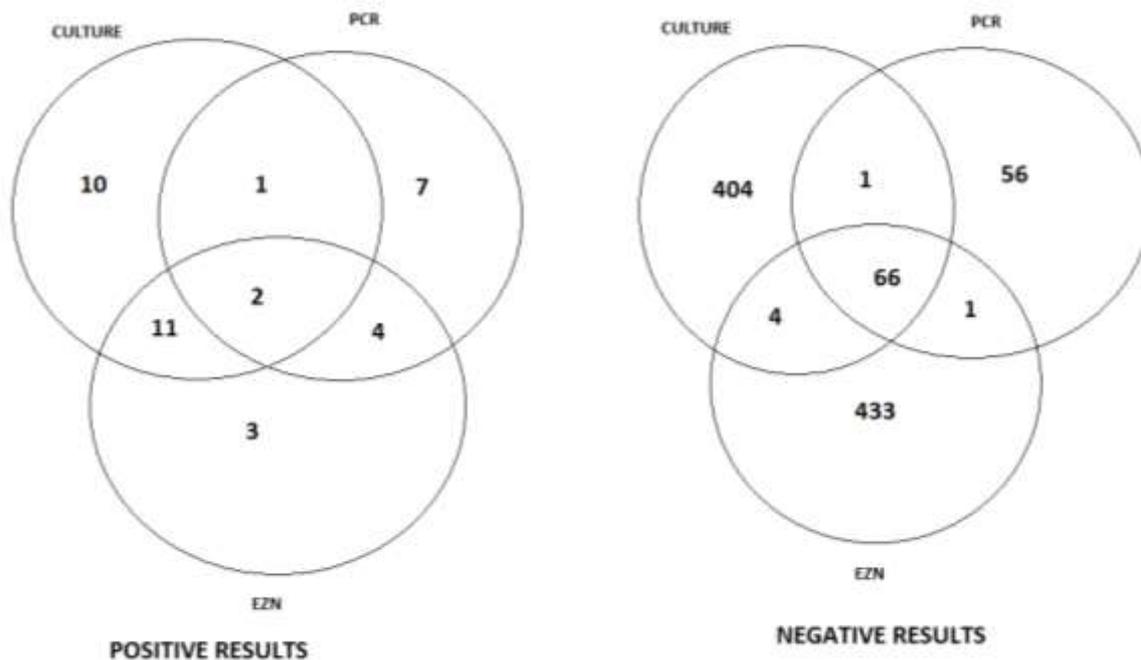
In total, of the EZN-positive samples, 30% were PCR-positive and 65% were culture-positive; of the culture-positive samples, 13% were PCR-positive and 54% were EZN-positive; of the PCR-positive samples, 21% were culture-positive and 43% were EZN-positive.

Statistically, all three tests (EZN, PCR, culture) were used in the evaluation of the samples. However, the numbers of the samples evaluated by each test differed from each other. Therefore, no statistical measures such as sensitivity, specificity, positive prediction value, and negative prediction value were used to evaluate the performance of each test. Moreover, considering that the significance of the difference among the rates would provide no valuable information regarding the performance of the tests, no comparison was performed for the resultant rates. On the other hand, since the primary aim of the study was to investigate whether the sequential order of the tests was appropriate and to develop an algorithm for the flow assay, no statistical test or comparison was performed throughout the study. This situation can be regarded as the limitation of the study and thus further studies are recommended to take this situation into account while establishing their research designs.

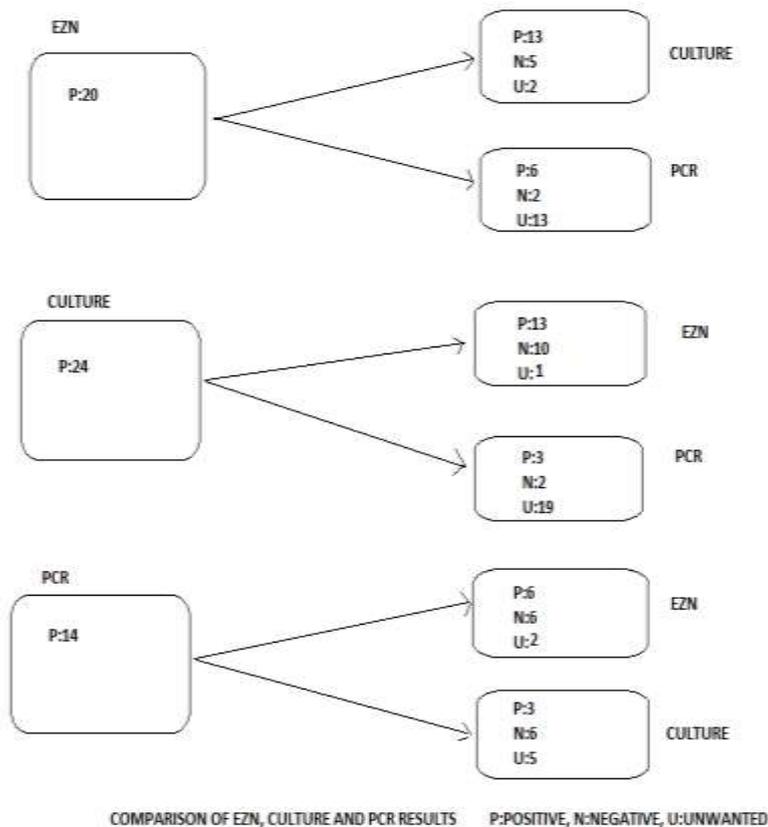
## Discussion

Microscopic examination and culture remain the methods of choice for the diagnosis of TB and the guidance of therapeutic decisions. Nucleic acid amplification and line probe assays speed up the identification and susceptibility testing of mycobacteria in AFB smear positive specimens or in culture (7-9). In our study, PCR was not required for 13 out of the 20 samples positive on AFB and for 19 out of the 24 samples positive on culture (Figure 2). Based on these results, it is obvious that PCR can be ignored for the *Mycobacteria* diagnosed by EZN and culture. Therefore, clinicians are likely to determine the diagnostic tests based on their own needs and thus may prefer not to use a standard algorithm.

The conventional EZN method on direct smears for AFB is widely used and plays a key role in the diagnosis and also in the monitoring of treatment (10). Although easy to perform and specific, it lacks sensitivity, requiring 10,000 bacilli.mL<sup>-1</sup> of sputum to become positive (12) with a sensitivity of 22% to 81% (10). Similarly, in a study conducted with EZN, the researchers found that the sensitivity and positive predictive values, in particular, were quite low (11). In our study, considering that culture is the gold standard, we found that almost half (10 out of 24) of the culture-positive samples were negative on EZN (Figure 2).



**Figure 1:** Combination of positive and negative results.



**Figure 2:** Comparison of EZN, Culture and PCR results [P: Positive, N: Negative, U: Unwanted (no request)]

Besides, Mycobacterial culture is the gold standard method for the detection of tubercle bacilli (70% to 80%), but it is time-consuming and requires specialized safety procedures and must be performed in a biosafety level 3 facility (10,11). It can detect 100 bacilli.mL<sup>-1</sup> of sputum in comparison with 5,000–10,000 bacilli.mL<sup>-1</sup> needed for microscopy. Following decontamination and liquefaction procedures, sputum samples are inoculated and incubated for morphological growth, which usually occurs after several weeks of incubation (12). As proposed by the algorithm, the samples can be evaluated using a sequential order of EZN, culture, and, if suitable laboratory conditions are available, PCR. In our study, the EZN was followed by culture, and the algorithm was established based on 524 EZN, 499 culture, and 138 analyses (Figure 1). At present, a number of elaborate culture systems are available commercially. Culture methods available today are sufficient to permit laboratories to develop an algorithm that is optimal for patients and administrative needs (13).

In a previous study, the responses obtained from 21 TB reference laboratories were reported. In 17 of the laboratories, the algorithms used to diagnose pediatric and adult TB patients did not differ, whereas four laboratories reported the use of extra tests for children. Most of the primary samples were subjected to smear microscopy, resulting in a 3.3% positivity rate. Culture was more often positive in non-respiratory samples than in respiratory samples. The sensitivity of molecular tests was significantly higher in smear-positive samples than in smear-negative samples (14). In this study, an algorithm was applied for all the samples sent to the laboratory. Respiratory and non-respiratory sensitivity of the culture can vary in the examples. PCR sensitivity of smear positive samples is higher. In our study, the rate of positive samples was higher than the negative samples on EZN. However, since PCR was not required in all positive samples, reliable results were not obtained at the end of the study. In addition, the rate of culture-positive samples among EZN-positive samples is high. Moreover, culture was required in most of the samples that required EZN.

Tuberculosis is globally controlled by low sensitive conventional diagnostic assays. The current gold standard for the diagnosis of tuberculosis is the combination of culture and clinical diagnosis. For rapid diagnosis of Mycobacterium tuberculosis, highly specific and sensitive assays are performed. Nucleic-acid amplification tests (NATs) support rapid diagnosis of TB, particularly in reference laboratories. Therefore, in addition to conventional diagnosis tests, which are time-consuming and labor-intensive and also insufficient for species-level identification, new solutions are required for the problems in routine diagnostic applications for tuberculosis (15).

## Conclusion

The results revealed that the samples positive on EZN are not necessarily positive on culture and PCR. Moreover, culture is the gold standard for confirming the diagnosis of Mycobacteria regardless of the positivity on EZN. PCR is a rapid diagnostic test which can be used for identifying the clinical status of the suspected cases. For this reason, the implementation of an algorithm can reduce the duration of diagnosis and also produce more randomized results. On the other hand, ignoring the algorithm and not performing the basic diagnostics steps may lead to serious diagnostic problems as well as loss of time and money.

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical issues:** All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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## Superficial fungal infections in children

Ayse Akbas<sup>1\*</sup>, Fadime Kilinc<sup>1</sup>, Halil Ibrahim Yakut<sup>2</sup>, Ahmet Metin<sup>3</sup>

### Abstract

**Objective:** This study was performed to determine the prevalence and the demographic characteristics of patients, who were diagnosed with superficial fungal infection at the dermatology department of two centers, and compare their epidemiologic data to those reported in the literature.

**Material and Method:** Files of 20716 children, between 0 and 16 years of age, who presented to the Dermatology Outpatient Clinic between 2011 and 2015, were investigated retrospectively. Of these, 518 children, diagnosed with superficial fungal infection, were assessed with respect to age, gender, presence of systemic disease and demographics. The diagnosis and the laboratory investigations performed were recorded

**Results:** There were 251 girls (48%) and 267 boys (52%), diagnosed with superficial fungal infection. Eight types of superficial fungal infection were detected in 518 patients (2.5%). Assessment by age group revealed the following: 8.4% of the infection were observed between 0 and 2 years of age (n=44), 16.9% were observed (n=88) between 3 and 5 years of age, 34.9% were observed (n=181) between 6 and 11 years of age and 39.5% were observed between 11 and 16 years of age (n=205). *Tinea corporis* (26%, n=136) and *Pityriasis Versicolor* (19%, n=99), *Candidiasis* (17%, n=86) and *Tinea Pedis* (14%, n=72) were the most commonly detected ones.

**Conclusion:** Superficial fungal infections occur less in children, promptness is important in the diagnosis and treatment due to potentially permanent complications. In addition, with respect to preventive medicine, being aware of the factors that would reduce transmission would prevent occurrence of complications.

**Keywords:** superficial fungal infection, children, prevalence

### Introduction

Superficial fungal infections (SFI) are common among children's skin disorders. 7-15% of the pediatric clinical manifestations result from SFI. The factors frequently include the *Trichophyton*, *Microsporum* and *Epidermophyton* species and they are transmitted via skin contact from humans, animals and the soil. The clinical course is determined by the host's immune response, localization and the type of the fungus (1). The distribution of the factors may vary depending on the country, geographic region, the climate and the living conditions. To avoid complications such as cicatricial alopecia and nail dystrophy, early diagnosis and onset of treatment is important. Factors that would reduce or prevent transmission should be known; and this is significant for preventive medicine (2). There is limited number of studies on pediatric SFI. In this study, we retrospectively investigated the incidence and distribution of pediatric cases, diagnosed with SFI.

### Material and Methods

Files of 20716 children, between 0 and 16 years of age, who presented to the Dermatology Outpatient Clinics of Ankara Pediatric Health and Diseases Hematology Oncology Training and Research Hospital and Ankara Atatürk Training and Research Hospital between 2011 and 2015, were investigated retrospectively. Of these, 518 children, diagnosed with SFI, were evaluated with respect to age, gender, presence of systemic disease and demographics. The diagnosis and the laboratory investigations performed were recorded. Patients were grouped by demographic data and diagnosis.

It was approved by the local ethics committee before start of the study. All patients were diagnosed by examination findings and fungal screening using a direct microscope with 10% KOH, to assist in diagnosis. Culture could not be conducted due to the difficulty of the procedure.

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1 Dept of Dermatology, Ministry of Health Atatürk Training and Research Hospital, Ankara, Turkey

2 Dept. of Pediatric Dermatology, Ministry of Health Ankara Child Health and Diseases Hematology Oncology Education and Research Hospital, Ankara, Turkey

3 Dept of Dermatology, School of Medicine, Yıldırım Beyazıt University, Ankara, Turkey

\* Corresponding Author: Ayse Akbas E-mail: [ayseakbas62@gmail.com](mailto:ayseakbas62@gmail.com) Phone: +903122171709



Patients were investigated under 4 categories to compare distribution by demographic data and diagnosis: between 0 and 2 years (infantile), between 3 and 5 years (pre-school), 6 and 11 years (school) and between 12 and 16 years (adolescence).

Statistical analyses were performed with SPSS Version-20; comparison of the categorical variables was done with Fisher Cross Table statistics and for determining statistical significance, Chi-square test was used.  $P < 0.05$  was considered significant. % was used for summarizing data

## Results

Among patients, diagnosed with SFI, 251 were females (48%) and 267 were males (52%). The male to female ratio was 1.08.

Eight types of SFIs were detected in 518 patients (2.5%). Among SFIs, *Tinea Corporis* (26%, n=136) and *Pityriasis Versicolor* (19%, n=99), *Candidiasis* (17%, n=86) and *Tinea Pedis* (14%, n=72) were the most commonly detected ones.

Assessment by gender revealed the following: 8.4% of the infection were observed between 0 and 2 years of age (n=44), 16.9% were observed (n=88) between 3 and 5 years of age, 34.9% were observed (n=181) between 6 and 11 years of age and 39.5% were observed between 11 and 16 years of age (n=205). Distribution by age group is shown in Table 2.

Investigation of the presence of the concomitant disease in children with SFI revealed different skin diseases at a rate of 2.3% (n=12) and non-skin diseases at a rate of 4.4% (n=23) (Table 3).

**Table 1:** The most common superficial fungal infection by gender in children. \* Percentage indicates the rate of the diseases by gender

The Diseases	Girl	%*	Boy	%*	Total
<i>T. Corporis</i>	54	40	82	60	136
<i>P. Versicolor</i>	52	53	47	47	99
<i>Candidiasis</i>	54	63	32	37	86
<i>T. Pedis</i>	27	38	45	62	72
<i>T. Capitis</i>	25	43	33	57	58
<i>Onychomycosis</i>	29	62	18	38	47
<i>T. Ingualis</i>	10	53	9	47	19
<i>T. Manum</i>	-	-	1	100	1
<b>Total</b>	251	48	267	52	518

**Table 2:** Distribution by age group

Diseases	Number of Patients	Overall %	In the Group	0-2 y		3-5y		6-11y		12-16y	
				N	%	N	%	N	%	N	%
<i>T.corporis</i>	136	0,66	26	4	9	20	23	65	36	47	23
<i>P.versicolor</i>	99	0,48	19	3	7	5	6	17	9	74	36
<i>Candidiasis</i>	86	0,42	17	20	45	26	29	25	14	15	7
<i>T.pedis</i>	72	0,35	14	2	5	6	7	28	16	36	18
<i>T.capitis</i>	58	0,28	11	6	13	21	24	26	14	5	2
<i>Onychomycosis</i>	47	0,23	9	7	16	7	8	8	19	19	8
<i>T.ingualis</i>	19	0,09	4	2	5	3	3	6	3	8	4
<i>T.manum</i>	1	0,005	-	-	-	-	-	-	-	1	1
<b>Total</b>	518	2,5	100	44	10	88	100	181	100	205	100

**Table 3:** Presence of concomitant disease in children with superficial fungal infection

Diseases	Concomitant Disease	Number of Patients
<i>Onychomycosis</i>	Obesity	1
	Down Syndrom	1
	Paronychia	1
	<i>T. Pedis</i>	1
	Hyperhidrosis	1
<i>T. Pedis</i>	Acne	3
	Elevated Liver Enzymes	1
	Asthma	2
	Cerebral Infact	1
	Kidney Abnormality	1
	Hypothyroidism	1
<i>T. Capitis</i>	Seborheic Dermatitis	2
	Acne	1
<i>T. Corporis</i>	Hypothyroidism	1
	Osteoporosis	1
<i>T. Faciei</i>	Milk Allergy	1
<i>T. Manum</i>	Epilepsy	1
<i>P. Versicolor</i>	Anemia	1
	FMF	1
	Osteoporosis	1
	Allergic Rhinitis	1
	Diabetes Mellitus	1
	Growth Retardation	1
<i>Candidiasis</i>	Congenital Cardiac Disease	2
	Frequent Urinary Infection	1
	Hyperactivity	1
	Degenerative Cerebral Disease	1
	Dermatitis	2
	Pyoderma	1

## Discussion

In children, SFI is not observed as commonly as in adults; but it has been gradually increasing and becoming remarkable over time due to its complications. Its pediatric incidence varies depending on the populations, geographic regions and different climatic conditions (3,4,5,6).

The rates were as follows: 13.4% in Ethiopia (7), 16.3% in Egypt (3) 2.3% in Switzerland (8), 35% in Nigeria (9), 4.65% in India (6), 6.7% in Kuwait (4). In our country, the rates vary between 3.8 and 6% in studies on SFI (10-12). In this retrospective study we performed in 20716 pediatric patients, we detected the incidence of SFI as 2.5%. These differences may result from environmental, geographic, hygienic differences and the number of patients. Karaca et al. detected that SFI was most common between the age of 5 and 12 (50%) (13).

In our study, we most commonly observed *T. Corporis*. *T. Corporis* involves the dermatophyte infection of the regions other than the groins, palms, and soles. In children, it is transmitted via pets and in the rural area, it is transmitted via bovine or ovine animals.

When it manifests on the face, it is called tinea facialis (14, 15).

In Nigeria, the ratio was reported to be 0.06% and in the trial by Ertas et al involving 51 cases, the ratio was reported to be 7.8% (9,16). In this study, we found *t. corporis* at a ratio of 26% in 136 children in total with 5 occurring on the face.

*Pityriasis Versicolor* is a yeast infection of the stratum corneum in the regions where sebaceous glands are located on the epidermis, which is caused by *Malassezia furfur*. It occurs as hypo- or hyperpigmented macula on different parts of the body in varying size in hot and humid climate. It involves the face uncommonly (15,17). While Nanda et al (4) reported a ratio of 0.62% and Oke et al (9) reported a ratio of 4.4%, in our country Seraslan et al (10) detected a ratio of 5.4%, Tamer et al (12) detected a ratio of 0.09% and Kavak et al reported a ratio of 2.5% (18) and they all declared that the disease increased with age. In similarity to the trial by Ertas et al, we detected an overall ratio of 0.48% and 19% in 518 children (16). The increase observed with the increasing age was statistically significant.

The higher incidence during adolescence may be attributed to hormonal causes.

*Candidiasis* is a fungal infection that is caused by *Candida Albicans*. In our study, its incidence ranked third among others. *Candida*, detected in 2-5% of the healthful babies, is present at a high ratio in oral flora and folds of the skin. The disease occurs as a result of physical irritation such as moisture, heat, friction, alkaline pH and diabetes, collagen tissue disorder, malignancy, severe infections, immunocompromising diseases, and presence of systemic predisposition such as AIDS (14,17,19). The prevalence of oral candidiasis varies between 0.1 and 37 (4, 14,20,21). In our country, Yilmaz et al reported the ratio as 10% below 2 years of age and Kose et al detected the ratio as 7.7% (22, 23). In our study, only 4 among 86 patients had oral Candidiasis and 6 had vaginal Candidiasis. While oral Candidiasis is not observed commonly in children, the low rate we detected in our study may be associated with the fact that this disease was solved by the parents, primary care physicians and pediatricians. In the study by Koksall et al. performed in children between 2 and 15 years of age, Candidiasis was reported at a ratio of 1% while Ertas et al detected a ratio of 15.8% (16,24). In our study, among all other diseases, Candidiasis was reported at a ratio of 0.42% and among fungal diseases, it was detected at a ratio of 17%. More than half were between 0 and 5 years of age.

*T. pedis* is reported between 1.3% and 2.3% and at a higher rate during adolescence. It was detected at a rate of 2.5% in a Spanish study (25); in a screening, performed in 7158 children between 6 and 14 years of age in Istanbul, the rate was detected to be 0.15 for *T.Pedis* (26); Balci et al reported a rate of 0.05 for *T.Pedis* in a screening of 8122 children (27). Inanir et al detected *T. Pedis* in 0.5 of 785 children (28). In our country, the rates in other studies range between 4.6 and 2.6% (11,18). In our study, we detected an overall rate of 0.35% in 72 children and a rate of 14% in the group for *T. Pedis*, similar to Tekin et al (29). These different ratios in the studies may be related to the fact that the studies were performed for the purpose of screening or to the examination of the patients, who presented to the clinic due to complaints.

In children, *T. Capitis* is a common dermatophyte infection (11,12). It is common in children between 2 and 10 years of age before puberty. In kerion forms, scar tissue may develop and lead to alopecia and represent a cosmetic issue for the individual (2,11). Contact with animals, poor hygiene conditions facilitate the occurrence of the disease. Based on the reports by the WHO, *t. capitis* has a rate of 7-13% and differs by the geographic region (30). In children, it occurs at a rate of 1% (30). The rate ranges between 0.07 and 0.8% in Turkish studies (3,12,14,24). In the foreign literature, the rates were as follows: 0.23% in

Spain, 26.9-62.5% in Nigeria, 68% in India and 78% in Egypt (3, 6, 9, 29). These results show that it is correlated with the level of development of countries. Ertas et al reported the *t. capitis* ratio to be 35.4 (16). Balci et al detected a *t. capitis* ratio of 0.03 in their screening involving 8122 students (27). In our trial, we detected an overall ratio of 0.28%, 11% among the SFIs, 24% between 3 and 5 years and at a higher ratio in males. Koksall et al reported a ratio of 54% between 2 and 15 years and at a higher ratio among males, similar to us (24).

*Onychomycosis* is the fungal infection of the nails and represents 20% of all nail diseases. It was reported at a rate of 0.2-2.6% (14). In children, the structural differences of the nail plaque or excessive exposure to recurrent traumas may represent an effective barrier for colonization of the fungal agents and this may explain why it is reported at a lower rate relative to adults (15,17,31). However thumb sucking habits, irritation caused by the saliva, and use of pools create a quite appropriate environment for fungus growth. Down syndrome, HIV infection, long term use of cortisone, presence of previous tinea pedis and tinea capitis are among the other risk factors (17). In our study, one of our patients had Down syndrome. The disease is caused by dermatophytes, yeast or mold. Mostly hands are involved in pre-school children and feet are involved at older ages (14,32). Early diagnosis and treatment is important in eliminating the source of the infection and avoiding nail dystrophy (2). Gupta et al found the ratio of onychomycosis was 0.44% (35) below 18 years and the ratio was 0.02% in the study reported by Philpot et al (33). Oke et al reported a ratio of 0.8% for onychomycosis while Sobjanek et al detected a ratio of 9.7 in a screening performed in 1588 children below 16 years in Poland (9, 34). Hapcioglu et al reported onychomycosis at the highest ratio (3.3%) (26). In this study in 23235 children between 7 and 14 years, the ratio was detected to be 0.01% (26). The ratios were between 0.10 and 3% in the other studies in Turkey (12,13,26,28,31). Balci et al detected onychomycosis in a pediatric screening involving 8122 children between 5 and 16 years of age (0.018) (35). Ertas et al told a ratio of 17.8% (16). In this study, we detected an overall ratio of onychomycosis of 0.23%; the ratio was 9% among the fungal infections and the condition was most common between 12 and 16 years and occurred more among girls.

*Tinea Inguinalis (Tinea cruris)*: It is more common in males. It manifests as an itchy plaque with a sharp edge, located laterally or bilaterally in the genito-crurale region (inner part of the femurs), which expands slowly (19). While Ertas et al reported only one case, we had 19 cases in our study (16).

*Tinea Manum* was present in only one case.

Atopic system predisposes the individual to transmission of the infection. While hypersensitivity to

the factors aggravates the infection, suppressed or deficient cellular immunity leads to chronic diffuse and refractory clinical courses (1). In our trial, we detected the systemic diseases such as asthma, allergy history, chronic infections, liver dysfunction, renal disease and epilepsy at a rate of 4.4% in 23 cases. In addition, history of drug use in relation to these diseases may have facilitated occurrence of SFI and complicated recovery.

As can be seen in Table 3, the presence of systemic diseases including congenital cardiac disease, frequent urinary infection, chronic dermatitis, degenerative brain disease facilitate the development fungal infections. Socio-economic status, malnutrition, poor hygiene also affect the pattern of the skin diseases.

## Conclusion:

Fungal diseases of childhood differ from those in adults with respect to type, distribution and incidence. While there are many studies in this age group, the results are not very satisfactory. If left untreated, some fungal infections can lead to permanent hair loss and nail dystrophies and impair quality of life. Different from the other studies in our country, this study involved a large series, which could provide a more accurate view on the incidence of the diseases. We believe that our study could initiate future studies and be helpful in preventive medicine.

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## Pregnancy outcome of a case with Swyer syndrome after bilateral gonadectomy and adjuvant chemotherapy

Cenk Gezer<sup>1\*</sup>, Atalay Ekin<sup>1</sup>, Alkim Gulsah Sahingoz Yildirim<sup>1</sup>, Ulas Solmaz<sup>2</sup>, Tugba Karadeniz<sup>3</sup>, Sevil Sayhan<sup>3</sup>, Mehmet Ozeren<sup>1</sup>

### Abstract

Swyer syndrome is a rare disorder characterized by a phenotypic female with an XY karyotype. We presented a patient with Swyer syndrome with a diagnosis of malignant germ cell tumour. After bilateral gonadectomy and pelvic lymph node dissection, the patient received four courses of bleomycin, etoposide and cisplatin chemotherapy. The patient was free from tumour recurrence after 13years' follow-up. A successful pregnancy was achieved by oocyte donation and in vitro fertilization. Caesarean delivery was performed at 37 gestational weeks due to oligohydramnios and intrauterine growth restriction.

**Key words:** 46, XY gonadal dysgenesis; chemotherapy; gonadectomy; pregnancy; Swyer syndrome

### Introduction

XY gonadal dysgenesis, known as Swyer syndrome, is a rare disorder characterized by phenotypically female with primary amenorrhea, tall stature, normal appearance of external genitalia, hypoplastic uterus, streak gonads and absence of secondary sex characteristics (1). Since gonads have no hormonal potential, diagnosis of this syndrome is usually made at adolescence. The current practice in Swyer syndrome is prompt removal of the dysgenetic gonads due to high risk of malignant tumour development. Furthermore, long-term combined oestrogen and progesterone therapy is recommended to induce puberty.

A number of successful pregnancies achieved by oocyte donation are described in the literature but cases with malignant germ cell tumours who received chemotherapy or radiotherapy have not been reported so far (2). Here, we report a successful pregnancy in a pure 46, XY gonadal dysgenetic woman with prior diagnosis of malignant germ cell tumour who underwent gonadectomy and received adjuvant chemotherapy.

### Case presentation

A 17-year-old female was referred to our department for primary amenorrhea. Detailed examination and investigation for the cause of primary amenorrhea was performed. Patient was of a female phenotype with a 165 cm height and 55 kg in weight.

The secondary sexual characteristics including breast development and pubic hair were at Tanner stage III. Female external genitalia were present without evidence of cliteromegaly. The vagina was patent, and there was a small cervix. Pelvic ultrasonography revealed a small uterus (5 x 1.7 x 2 cm) and bilateral adnexal masses with the right side measuring 12 x 12 x 9 cm and left side measuring 10 x 11 x 8 cm (Fig. 1). Intravenous pyelography revealed normal urinary system anatomy and normal functioning kidneys accompanying a small bladder stone. Karyotype analysis demonstrated 46, XY genotype. Hormone levels revealed elevated serum follicle stimulating hormone (65 mIU/mL) and luteinizing hormone (24 mIU/mL) concentrations, a very low estradiol level (14 pg/mL), a normal total testosterone (23.02 ng/dL) and a low free testosterone level (0.08 pg/mL). Results implied primary gonadal failure in a phenotypic female with a male genotype. Tumour markers including CEA,  $\beta$ -hCG, CA-125, CA 19-9, CA 15-3 and AFP were within normal limits.

Laparotomy demonstrated a hypoplastic uterus, normally developed fallopian tubes and bilateral adnexal tumours, which confirmed our diagnosis of pure gonadal dysgenesis. There was no evidence of local or distant metastasis found during the operation. Bilateral gonadectomy and pelvic lymph node dissection were performed.

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1 Dept of Perinatology, Izmir Tepecik Training and Research Hospital, Izmir, Turkey

2 Dept of Oncology, Izmir Tepecik Training and Research Hospital, Izmir, Turkey

3 Dept of Pathology, Izmir Tepecik Training and Research Hospital, Izmir, Turkey

\* Corresponding Author: Cenk Gezer E-mail: [drckenkgezer@gmail.com](mailto:drckenkgezer@gmail.com) Phone: +90 232 433 0608





**Figure 1:** The gross appearance of left ovarian dysgerminoma arising from gonadoblastoma. Note the solid and lobulated surface of gonadoblastoma (white arrow).

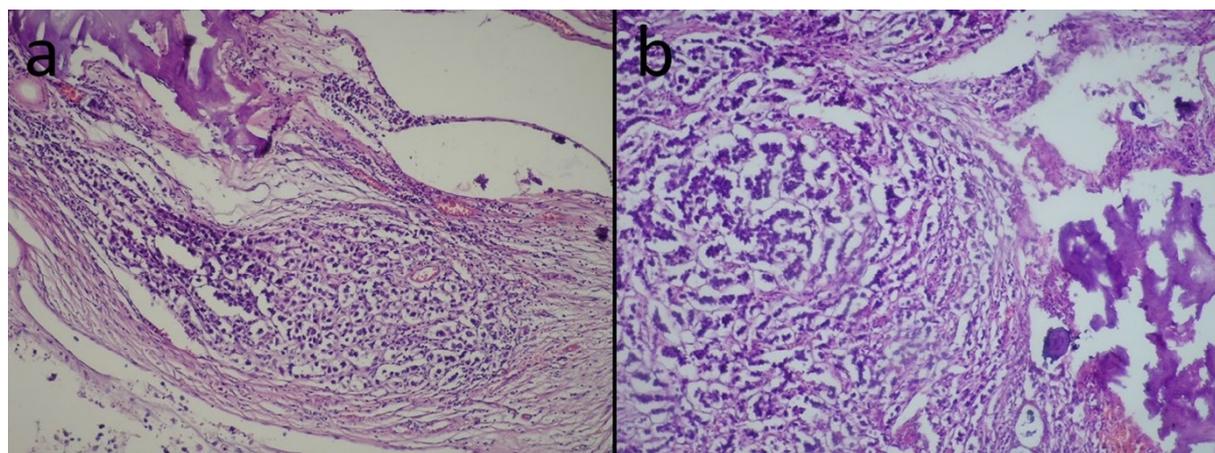
Para-aortic lymph node dissection was not performed due to Pfannenstiel incision and existing controversies regarding optimal management of germ cell tumours at the time of surgery. Histopathologic examination documented gonadoblastoma on the right streak gonad and gonadoblastoma accompanied by dysgerminoma on the left gonad (Fig. 2). Dysgerminoma was spread beyond the ovarian capsule and leiovascular space invasion was present. However, none of the lymph nodes showed a malignancy. After surgery, patient received four courses of adjuvant chemotherapy including bleomycin, etoposide and cisplatin. Cyclic oestrogen-progesterone therapy was also started. Postoperative period was uneventful and no recurrence was noted in the follow-up period. Thirteen years after initial diagnosis and at the age of 30 years she underwent in vitro fertilization with donated oocytes. Four fresh embryos were transferred and intrauterine presence of one live foetus noted at 6 weeks. Oestrogen and progesterone treatment was continued during the first trimester of pregnancy. Antenatal period was uneventful until 32 weeks of gestation, later on oligohydramnios has occurred with signs of foetal growth restriction. The Doppler analysis of umbilical and middle cerebral arteries was normal. Antenatal foetal surveillance with non-stress test and Doppler ultrasonography was continued every week until 37 gestational weeks and a healthy male neonate weighing 2460 gr was delivered by caesarean section. Both mother and neonate were discharged with no complications.

## Discussion

Although Swyer syndrome was described in 1955, first successful pregnancy in a patient with this syndrome was reported about 20 years ago (3). Immense progress in the field of assisted reproduction techniques helps to obtain intact pregnancies in these patients. However, at present, the number of pregnancies with Swyer syndrome is too small to answer several questions regarding maintaining pregnancy and delivery.

Early diagnosis of the Swyer syndrome is crucial because of tumour transformation in the streak gonads and initiation of oestrogen therapy. Approximately 15 to 35% of females with pure gonadal dysgenesis develop gonadoblastoma (4). These are benign tumours arising from persisting undifferentiated gonadal tissue, which have no metastatic potential. The importance of this benign tumour is its potential to be the precursor of other germ cell malignancies such as dysgerminoma, embryonal carcinoma, yolk sac tumour and teratoma. Therefore, prompt surgical removal of dysgenetic gonads is advised after the diagnosis because the risk for malignant transformation increases with increasing age. In some cases, however, first manifestation of the disease can be the malignancy itself. Michala et al. reported that two of the 29 patients were first presented with malignancy before the diagnosis of XY gonadal dysgenesis (5). In our case, we performed bilateral gonadectomy to avoid future malignancies and also to preserve uterus in consideration of fertility. Continuous hormone treatment should be initiated following the diagnosis, especially if gonadectomy is performed. Supplementation of sexual hormones can induce regular menarche and also prevent osteoporosis.

Since women with Swyer syndrome do not produce germ cells, the only way to get pregnant is treatment with donor oocytes. Hormone treatment is needed to prepare the uterus for embryo implantation and should be continued during the first trimester of pregnancy. A few cases of successful pregnancies after oocyte donation and in vitro fertilization have been reported in the literature (6-13). When considering antenatal surveillance, patients with Swyer syndrome should be evaluated separately from patients having a 45,X cell line who are increased risk for aortic dissection and rupture during pregnancy (14). Although most of the pregnancies in women with Swyer syndrome were uneventful, some of them were complicated by unfavourable perinatal outcomes. Creasas et al.(7), Kan et al.(8), Sauer et al.(9), and Ko et al.(10) observed hypertensive diseases in their cases with Swyer syndrome.



**Figure 2: (a):** Dysgerminoma is characterized by nests of round germ cells with vacuolated clear cytoplasm and large calcifications; Haematoxylin-eosin, x200 **(b):** Dysgerminoma consists of nests and cords of tumour cells and divided by occasional fibrous bands with lymphocytes; Haematoxylin-eosin, x100

Unlike others, Creatsas et al.(7), diagnosed blood pressure elevation in first trimester of pregnancy. Tulic et al.(11) reported reduced amniotic fluid at 39th week of gestation. Fedder et al.(12) presented a case of uterine rupture at 19 weeks of gestation in a patient with Swyer syndrome. They attributed this catastrophic event to the weakness of the uterine wall.

Preconceptional chemotherapy and radiotherapy is another (major) concern in women with malignant tumours and fertility desire. These adjuvant therapies found to be associated with increased preterm labour risk (15). None of the published reports of Swyer syndrome described a pregnancy after treatment with chemotherapy or radiotherapy for malignant germ cell tumours. Chen et al. reported a successful pregnancy in a patient with gonadoblastoma and accompanying mixed germ cell tumour but in their case they opted not to use adjuvant treatment because of aforementioned concerns (2). Our patient received four courses of bleomycin, etoposide and cisplatin therapy for treatment of dysgerminoma and any related side effects or any foetal anomaly was not observed. The only pathological event was the reduced amniotic fluid and late onset growth retardation without any other signs of foetal distress. In addition, no malignancy recurrence was noted in 13 years' of follow-up period

As in our case, caesarean section was chosen as the method of the delivery in most of the cases. One of the possible reasons for the relative high prevalence of caesarean delivery in patients with Swyer syndrome is the android shape of pelvis which may predispose them to abnormalities of labour. Another reason is that uterine size in 46, XY patients tend to be smaller than the normal population (4). It is suggested that hormone receptors which react to prostaglandin and oxytocin may be deficient in hypoplastic uterus.

However, there is no evidence that vaginal delivery should be avoided. Siddique et al. and Michala et al. reported successful vaginal deliveries in their cases, suggesting that normal uterine function including vaginal delivery is possible in patients with Swyer syndrome (5, 13).

In summary, we presented the case of first known successful pregnancy achieved in a patient with Swyer syndrome after chemotherapy along with bilateral gonadectomy. Although achieving a pregnancy in the absence of ovaries is common in contemporary medicine, our case revealed the significance of conservative surgical management even in advanced stage diseases. It should be noted that increasing survival rates in patients affected by oncological disease and advances in reproductive medicine have led to the development and increasing use of various fertility preservation techniques.

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**Ethical issues:** All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

**Acknowledgement:** Role of Authors: **AE:** Data collection, Manuscript writing/editing. **AGSY:** Manuscript writing/editing. **US:** Manuscript writing/editing. **TK:** Data collection, Data analysis. **SS:** Data collection, Data analysis. **MO:** Manuscript Editing

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## Primary small B cell non-Hodgkin Lymphoma of the Lacrimal Sac Upon Chronic Dacryocystitis

Murat Gumussoy<sup>1\*</sup> Sinan Uluyol<sup>1</sup> Gokhan Kurtoglu<sup>1</sup> Tolga Kandogan<sup>1</sup> Ibrahim Cukurova<sup>1</sup>

### Abstract

**Objective:** Primary non-Hodgkin lymphoma of the lacrimal sac is an extremely rare tumor. In this article, we report a 44-year-old female who was referred for dacryocystorhinostomy with complaints of epiphora and swelling on the right lacrimal sac region. She had slight epiphora for 8 years, which increased within 6 months, with concomitant swelling between the eye and the nose. A hard and fixed mass was detected on palpation just below the medial canthus. Magnetic resonance imaging showed a 30x35 mm tumoral, lesion which invaded the medial wall of the right orbit and compressed the medial rectus muscle. Histopathologic examination of the tumor revealed a small B cell non-Hodgkin lymphoma. As a conclusion, we suggest that if symptoms of a chronic dacryocystitis patient deteriorates, malignancy should be suspected

### Introduction

Malignant tumors of the lacrimal sac are unusual and most of them are epithelial tumors. Primary non-Hodgkin lymphomas (NHL) of this area are extremely rare[1-3]. These patients have symptoms like epiphora and swelling in periorbital region. Early suspicion and immediate biopsy are prerequisites for the diagnosis of malignancies in this area.

We present a patient with primary B cell NHL of the lacrimal sac developed secondary to chronic dacryocystitis and reviewed literature. To our knowledge it is the first case that primary lymphoma of the lacrimal sac was developed secondary to chronic dacryocystitis

### Material and Methods

Forty-four years old female patient with complaints of epiphora on the right eye for eight years and a growing mass in the right periorbital region for six months referred to our clinic with preliminary diagnosis of chronic dacryocystitis.

Physical examination revealed a firm, non-tender and irregular mass extending from medial canthus through nasolabial sulcus and lateral nasal cavity (Picture 1).

Endoscopic nasal examination revealed hyperemic mucosa with edema at the level of lacrimal sac.

In the ophthalmologic examination, there was no drainage through right nasolacrimal system by irrigation, and eye movements were within normal limits.

Anterior segment, optical disc, macula and visual examination were found within normal limits in both eyes.

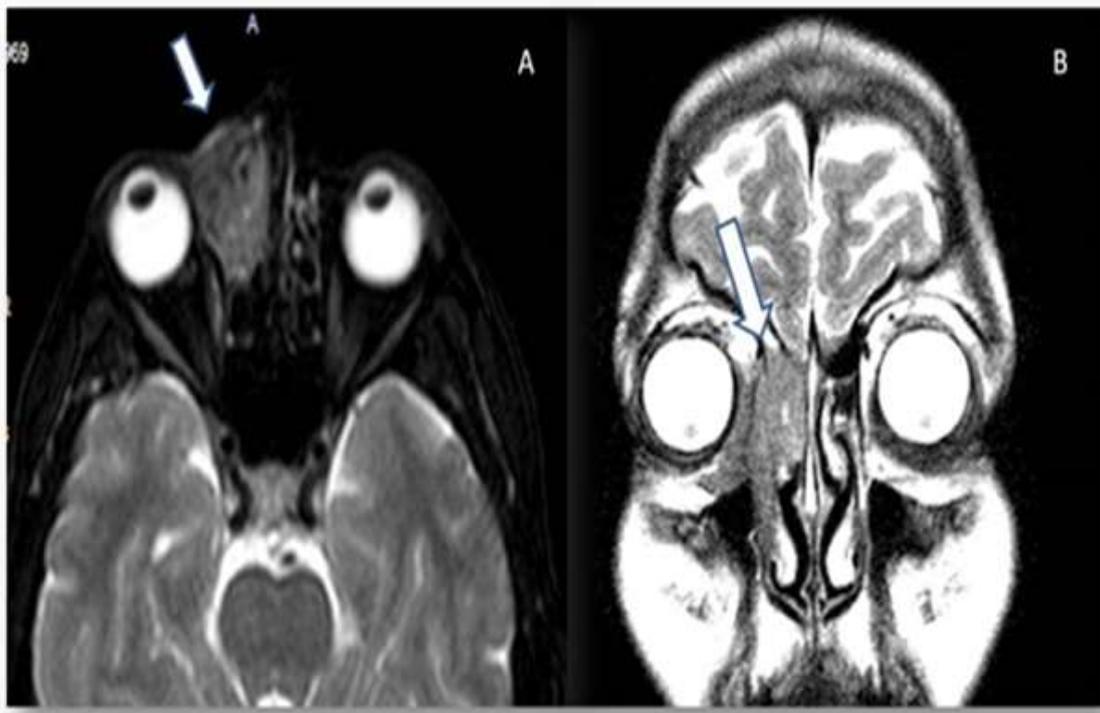


**Picture 1:** Physical examination (right eye and solid mass involving the lacrimal sac region)

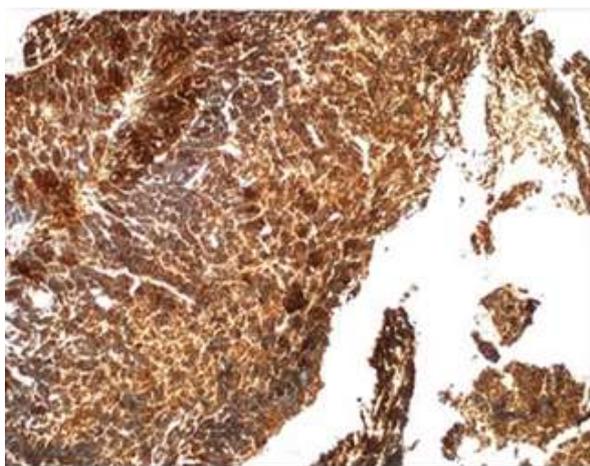


Magnetic resonance imaging scans showed a mass of 30 x 35 mm in size, invading the nasal side of the right orbita, including the right nasolacrimal duct and continuing to the level of inferior nasal concha. Compression of the medial rectus muscle was observed. Other structures were normal in right orbita (Picture 2).

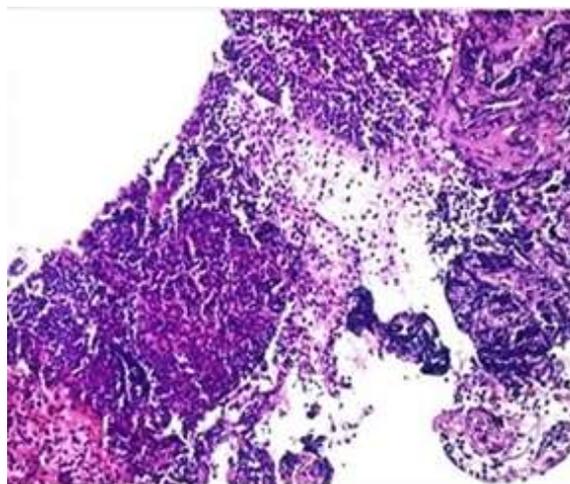
Multiple incisional biopsies were made from the mass and sent to pathology department. Histopathological examination of the specimens revealed a mixture of small to medium sized, mildly atypical uniform lymphocytes (Figure 3A, B).



**Picture 2:** Magnetic resonance imaging (coronal and axial) revealed a 30 X 35 mm solid mass involving the right lacrimal sac region.



**Picture 3A** Hematoxylin-eosin staining, monotonous, round-to-oval nuclei, indistinguishable from the cytoplasm tumor cells (second) (H&E, X400)



**Picture 3B** Diffuse membranous staining lymphocytes with CD20, X100 (CD20;Immunohistochemistry for the B-cell Marker.)

Immunohistochemically, tumor cells were negative for TTF1, NSE, synaptophysin, chromogranin and positive for leukocyte common antigen. The lymphoid cells were strongly and diffuse positive for CD79a, CD20, bcl-2 and negative for CD3, CD45Ro (Figure 3B). Histopathologic and immunohistochemical findings revealed a small B cell non-Hodgkin lymphoma.

Afterwards, whole body scans were performed and the patient was found free of any metastasis. The patient was treated with CHOP regimen chemotherapy (CT) for 8 cycles. Two months after the end of chemotherapy, only moderate epiphora was observed during physical examinations.

## Discussion

Lymphoma arising in the lacrimal sac is extremely rare. In literature, nearly 50 cases of primary lacrimal sac lymphoma have been described over a period of 30 years. Primary neoplasms originating from lacrimal sac are epithelial (75%) or non-epithelial (25%) tumors, such as mesenchymal tumors (12%), melanoma (5%), and malignant lymphomas (6%). [1-4] Carlin and Henderson [1] reported the median age at onset to be 51 years for lacrimal sac lymphoma. Primary nasolacrimal duct lymphoma is more common in females [3,4]. Predominant symptoms of lacrimal sac lymphoma are epiphora and swelling like acute attack of chronic

dacryocystitis [1-3]. Blood in the tears has been reported only once. Our case was a forty-four year old female patient with complaints of epiphora on the Eye Study (6). However, a insignificant increased risk of cortical cataract (5) and posterior subcapsular cataract (6) were also reported in these studies respectively in a similar way to our results. Our study differs from these trials with our cataract assessment technique and in our opinion this is one of the strengths of our study. Having not been using data from medical records, we may have reduced the risk of "misclassification bias". Sure, encountering with some artefacts in the LD analysis process is possible but we have tried to avoid from these artefacts by using a standardization method in the measurement procedure.

Nonetheless, some factors such as back scattering of light from the anterior lens area, shadows and light attrition may decrease the amount of light transmitted to the posterior pole of the lens and this may have caused nuclear and posterior area to appear less dense (26). Another limitation of the current study is that it is a not prospective cohort study. We have performed two-way ANOVA, ANCOVA and multiple regression analysis in order to evaluate the effect of gender and age on LD. Although statin use was still found to be more effective on LD than age and gender, our results may have been influenced by some other unpredictable factors.

Publication	Age	Sex	Symptoms	Pathological Diagnosis	Treatment	Follow-up /Months
Palamar M. [9]	55	F	Epiphora	DLBCL	CHOP	Alive/25
Kajita F [10]	77	M	epiphora and swelling	DLBCL	RT (30.6 Gy total dose)	Alive/12
Chai CK [11]	72	F	epiphora and swelling	DLBCL	Surgery first After recurrence CHOP	Alive/12
Maharajah KR [12]	60	F	epiphora and swelling	Small-B-cell lymphoma	Fudorubin cyclophosphamide	Ex (pulmonary embolism)
Gao HW [13]	41	F	epiphora and swelling	DLBCL	CHOP	Alive/14
de Palma P [14]	72	F	epiphora and swelling	DLBCL	CHOP first. After skin recurrence CHOP and VEP	Ex (heart failure)
Ustaalioglu BB [15]	65	M	epiphora and swelling	Small Lymphocytic lymphoma	Surgery	Alive/8
Schefler AC. [17]	10	M	epiphora and swelling	MALT lymphoma	Excisional surgery first, than chemotherapy	Alive/30
Köksal Y. [16]	9	F	Swelling	DLBCL	Excisional surgery first, than chemotherapy	Alive/12
Our case	44	F	epiphora and swelling	Small B-cell lymphoma	CHOP	Alive/24

We have excluded the patients with any refractive errors within  $\pm 3$  diopters spherical equivalent and any systemic diseases such as diabetes mellitus, hypertension and connective-tissue diseases. Nevertheless, we know that anti-hyperlipidemic treatment is used for cardiovascular disorders and the patients usually have comorbidities. Surely, some factors like these may have affected our results right eye for eight years and a growing mass in the right periorbital region for six months, and pathological diagnosis of the tumor was lymphoma. This case is consistent with literature as the age and complaints of the patient, and also pathological diagnosis being more frequently seen in female patients.

Primary lymphoma of the lacrimal sac is usually B-cell origin. Majority of B cell lymphomas are diffuse large B cell lymphomas (DLBCL) that runs an

aggressive course but potentially curable [6]. The other common group is mucosa associated lymphoid tissue (MALT) type lymphomas. Only 1 case of natural killer T- cell lymphoma (NK/T-cell type) was presented before. Its prognosis is worse than the others [7]. Our case was small B cell lymphoma but biopsy specimen size was not enough for subtyping.

The treatment modalities consist of surgery, radiotherapy (RT), CT or a combination of both. RT and/or CT are considered as the primary and definitive treatment [3-5]. Extensive surgery is avoided for functional and cosmetic preservation of the eye [6,7].

In order to obtain a biopsy we used transnasal endoscopic approach to prevent skin spread of the tumor and cosmetic deformity. After the histopathological diagnosis of NHL, the patient was given a CHOP regimen of 8 cycles similar to current approach.

Most common pathology of previous ten years cases was DLBCL (60%). One of them were small B-cell lymphoma like our case and one of them was MALT lymphoma. Chai CK[11] et al. performed surgery and after one year follow up when local recurrence occurred at hard palate level, they gave 6 cycles of CT. Kajita[10] et al. proposed RT and their patients underwent RT with 30.6 Gy in total dose. Cases of Scheffler[17] et al. and Koksall[16] et al. were in childhood age. Both authors preferred CT regimens after excisional surgery. Ustaalioglu[15] performed surgery alone as a treatment. The other authors preferred CT, mostly CHOP protocol. Two patients treated with CT protocols died also because of systemic factors. Except these two patients no evidence of recurrent tumors has been seen for any other patients with a mean follow-up of 17 months and these treatments have controlled the disease successfully without medical complications. Generally there was no significant difference in survival rates

between RT and CT and five year overall survival rate of patients were 80 % [9 -17] (Table 1).

The major adverse factors that affect the prognosis of primary lymphoma of nasolacrimal duct seem to be clinical stage and histological type[6-8]. Our patient was treated with CT and at 24 months follow-up she was alive and free of the disease. There was only one case of small B-cell lymphoma of nasolacrimal duct was reported before and that case died of other causes (pulmonary thromboembolism). So for this histological subtype there is not enough data on survival in comparison to our case.

## Conclusion

Lymphoma of the lacrimal sac is an extremely rare tumor. Suspicion and immediate biopsy are prerequisites for the early diagnosis of malignancies in this area. Otorhinolaryngologists and ophthalmologists must be aware of lacrimal sac tumors in patients with epiphora and rapid swelling.

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical issues:** All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

**Acknowledgement:** Role of Authors: **MG:** Data collection, Manuscript writing/editing. **SU:** Manuscript writing/editing. **GK:** Manuscript writing/editing. **TK:** Data collection, Data analysis. **IC:** Data collection, Data analysis, Manuscript Editing

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