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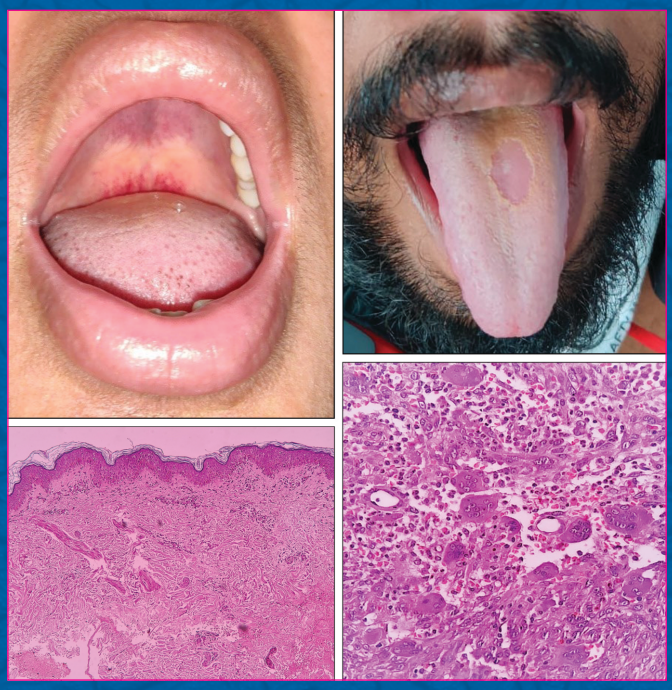

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Original Article

A Study of Cutaneous Manifestations of COVID-19: An Indian Perspective

Suyog S. Dhamale, Amit Jain, Snehal B. Lunge, Vijay Adhe, Vidyadhar R. Sardesai, Sujata V. Rege[1]

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Abstract

Background: Coronavirus disease-2019 (COVID-19) has been shown to involve multiple-organ systems during disease process. Dermatologists have also reported various findings in patients of COVID-19 and have pointed out few cutaneous manifestations that are novel and are probably related to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, currently very limited data are available regarding various aspects of cutaneous involvement. **Aims:** This study aimed to investigate various aspects of cutaneous involvement in COVID-19. **Methods:** Institutional ethics committee approval was secured before conducting a study. Patients with at least one positive nasopharyngeal swab result for SARS-CoV-2 carried out by reverse transcription polymerase chain reaction (RT-PCR) were enrolled. After informed consent subjects were interviewed and monitored for appearance of any cutaneous signs and symptoms. Those with relevant findings were evaluated for characteristics of cutaneous findings. Data of all patients were collected and analyzed. **Results:** A total of 303 patients were enrolled for the study. Approximately 1.98% of patients developed cutaneous manifestations. Four types of skin lesions were observed in study subjects: urticarial lesions, maculopapular rash, acro-ischemia, and glossitis. **Limitations:** Relatively less number of patients, collection of data from single center, and absence of histopathological confirmation were limitations of the study. **Conclusion:** COVID-19 disease process has a cutaneous component; however, incidence of cutaneous findings remains low. Urticaria was the most common type of cutaneous finding, whereas acro-ischemia was the most characteristic one.

Keywords: Acro-ischemia, COVID-19, cutaneous manifestations, SARS-CoV-2, urticarial lesions

Introduction

Toward the end of 2019, an outbreak of previously unseen pneumonia cases was reported from Wuhan, China.[1]

A novel coronavirus "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) was identified as a causative agent for this outbreak.[2]

The virus rapidly spread around the world and on March 11, 2020 World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) as a pandemic.[3]

As the pandemic progressed, dermatologists started to investigate possible cutaneous involvement in patients with COVID-19. As a result, various case reports and review articles started pouring in, describing the possible scope of cutaneous involvement in patients with COVID-19.[4-7]

However, to the best of author's knowledge only few studies have been conducted in this regard.[5] As for India, currently there is only one published study about cutaneous manifestations in Indian patients.[8]

Currently, there are limited data available regarding incidence and characteristic clinical features of skin lesions (if any) in patients with COVID-19. Also, the association of various clinical parameters of patients with skin lesions remains unclear.

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We planned to conduct a study to investigate above aspects as it may prove to be useful in patients which are otherwise asymptomatic except presence of skin lesions and refer them for diagnostic tests to rule out SARS-CoV-2 infection.

COVID-19 has been shown to involve multiple-organ systems during the disease course by various mechanisms.[9] During the conduct of this study, we sought to find out if it has any cutaneous component? If cutaneous findings are present, then what are its characteristics?

Are there any defining cutaneous manifestations for COVID-19 which can be used for identifying potential undiagnosed cases or prognosticating already diagnosed cases so as to help managing physicians to take clinical decisions?

Methodology

This study was conducted in a tertiary care center (designated COVID-19 care center) in western India. The study was conducted after getting approval from the institutional ethics committee (ethics committee approval number: BVDUMC/IEC/13). Ours was an observational study.

We enrolled the patients who were diagnosed with COVID-19 and admitted at our institute for management. Written informed consent was obtained from all participants or next of kin (in case of minors or critical patients).

We only included the patients with at least one positive real-time reverse transcription-polymerase chain reaction (RT-PCR) result for SARS-CoV-2 in nasopharyngeal swab sample and subsequently admitted for further management at our center.

Patients with clinical suspicion of COVID-19 but negative RT-PCR test were excluded. Participants who were not willing for consent were also excluded.

Methods

Eligible participants in study duration were enrolled.

Written informed consent was obtained from the patients.

Demographic and Baseline characteristics of the participants were recorded in the predesigned proforma.

General condition of the patient, cutaneous findings if any, clinical, epidemiological and laboratory parameters of the patient were noted at the time of admission in the ward/ intensive care unit.

On admission all participants were enquired for cutaneous lesions of recent onset (previous 2 weeks), if any.

Participants who had relevant positive history were subjected to cutaneous examination to note for characteristics of rash. The skin lesions were noted and photographed for purpose of documentation and follow-up. The evolution of rash was followed up till the final outcome of patient for COVID-19.

Rest all participants who did not have history of any rash were kept under monitoring for appearance of relevant skin lesions in the duration of their admission.

We collected clinical records of all study subjects.

In addition, we also interacted with patients who were clinically stable, to gather information about appearance of any relevant skin lesions of new-onset in the last 2 weeks. If found relevant, the data were collected and entered.

For patients admitted in intensive care unit (ICU) clinical records were the main source of data for us. Whenever possible next of kin were interacted with for any additional information. However, reliability of data obtained from relatives was limited.

Unfortunately, we could not conduct biopsy for any of the patients owing to difficulty in accessing the patients and possibility of contracting infection by health care workers.

Statistical analysis

All statistical analysis was carried out by Statistical Package for the Social Sciences (SPSS) software program, version 25.0. Continuous variables results shown by descriptive statistics and categorical variable results were shown by frequency and percentages. Student's t test was used for continuous variables with normal distribution and Mann–Whitney U test was used for continuous variables with abnormal distribution. Throughout results, 5% level of significance was used. All results were shown with 95% of confidence. A value of $P < 0.05\%$ was considered statistically significant.

Results

During the course of our study, we enrolled a total of 360 patients. Of those 303 patients could be included in the final data. The mean age of the study group was 40.25 ± 16.17 years. Clinical characteristics of the entire group of patients are as mentioned in Table 1.

During our study we found 2.64% (n = 8) had cutaneous complaints.

However, on evaluation 1.98% (n = 6) patients had cutaneous findings which were attributable to COVID-19.

Table 1: Clinical characteristics of patients in entire study group

No. of patients	Sex		Mean age	Systemic symptoms										
	M	F		Fever	Chills	Cough	Sore throat	Dyspnea	Muscle Pain	Abdominal pain	Diarrhea	Nausea/ vomiting	Anosmia	Cutaneous problem
303	65%	35%	40.25±16.17	45.87%	9.57%	41.91%	12.21	24.75%	13.2%	3.30%	4.95%	3.30%	0.33%	1.98%

The male-to-female ratio of patients with cutaneous complaints was 5:1. Clinical characteristics of patients who developed skin lesions are as per [Table 2].

We observed the following four types of lesions in our subjects.

Urticarial lesions

These were the most common type of lesions in our patients. Of 6 patients 50% (n = 3) patients had urticarial lesions. The lesions predominantly involved trunk. In one patient, lesions were also present on face. All patients responded to oral antihistamines promptly [Figure 1].

Maculopapular rash

Approximately 16.7% (n = 1) was found to develop maculopapular rash. On day 1 of fever patient developed mildly erythematous rash which blanched on pressure. The rash was asymptomatic and subsided with oral antihistamines within 24 h.

Acro-ischemia

We encountered one patient with findings suggestive of acral ischemia. The patient was 51-year-old man with history of hypertension. He was diagnosed with COVID-19 and was admitted for management. He recovered uneventfully and was discharged. One day after his discharge he again visited the facility with complaints of bluish discoloration and throbbing pain in right foot and toes. No past history of similar complaints was present. On further evaluation pulsations of ipsilateral dorsalis pedis artery were not palpable. On laboratory evaluation D-dimer levels were found to be raised (1038 ng/mL, > 4 times the normal levels). Patient also had findings of hypokalemia and raised C-reactive protein (CRP) levels. The diagnosis of right sided dorsalis pedis thrombosis was ascertained. Patient was again admitted and managed in consultation with vascular surgeon. He was administered low molecular weight heparin, cilostazol. Patient rapidly recovered and was discharged.

Glossitis

One patient (16.7%) reported complaints suggestive of oral mucositis during the course of admission. On examination features suggestive of glossitis were observed [Figure 2]. No past history of similar complaints in the past could be elicited. Patient was managed symptomatically.

Clinical characteristics of the patients with COVID-19 with cutaneous findings are provided in Table 2.

Table 2: Clinical information of COVID-19 patients developing cutaneous lesions

	Urticarial lesions	Maculopapular rash	Acro-ischemia	Glossitis
No. of patients	50% (n = 3)	16.7% (n = 1)	16.7% (n = 1)	16.7% (n = 1)
Sex				
M	3	0	1	1
F	0	1	0	0
Age	46 year; 56 years; 62 years	26 years	51 years	23 years
Systemic symptoms				
Fever	66.66%	100%	100%	100%
Chills	0	100%	0%	0
Cough	33.33%	100%	100%	100%
Sore throat	0	100%	100%	0
Dyspnea	0	0	100%	0
Muscle pain	0	100%	0%	100%
Abdominal pain	0	0	0%	0
Diarrhea	0	0	0	0
Nausea/vomiting	0	0	0	0
Anosmia	0	0	0	0
Cutaneous symptoms	Itching (100%)	Asymptomatic	Pain at local site	Burning
Comorbidities	DM (33.33%)	None	HTN	0
Duration of rash	1day; 1 day; 3 days	1 day	1 day	1 day
Drugs given				
Paracetamol	100%	100%	100%	100%
NSAID's	0	0	0	0
Hydroxychloroquine	0	0	0	0
Corticosteroids	0	0	0	0
Azithromycin	66.66%	100%	100%	0
Oseltamivir	66.66%	100%	100%	0
Amoxicillin-clavulanic acid	0	0	0	0
Any other drugs	Multivitamins, antihistamines	Multivitamins, antihistamines	Aspirin, cilostazole, LMWH, amlodipine	Multivitamins

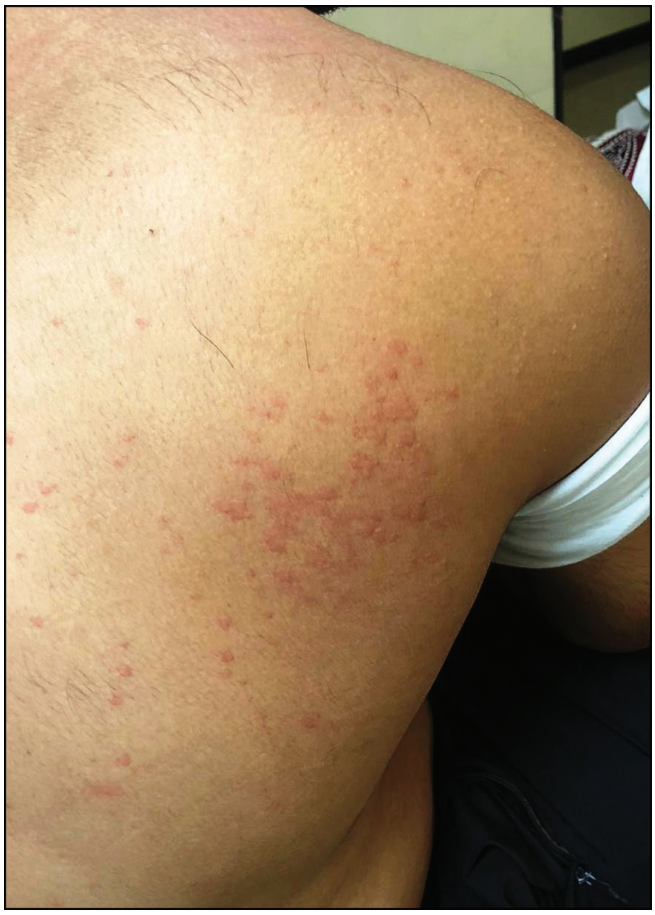

Figure 1: Urticarial lesions on back in patient with COVID-19

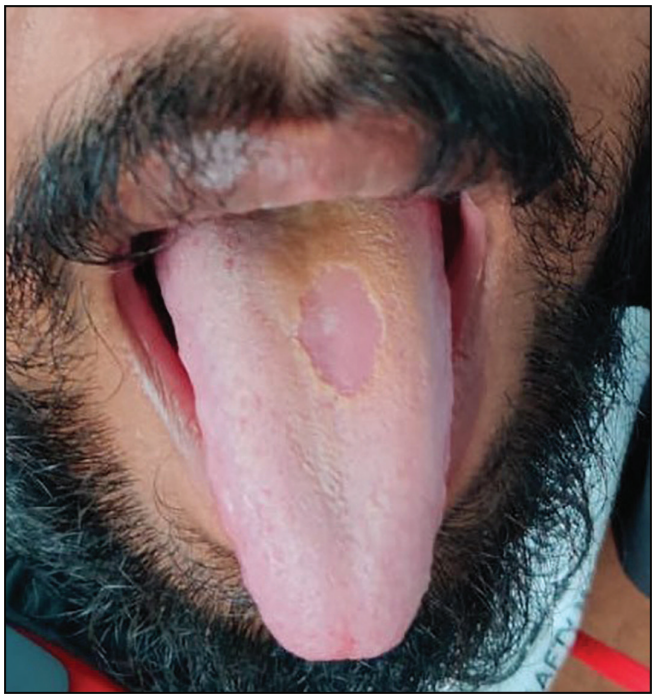

Figure 2: Lesions of glossitis in patient with COVID-19

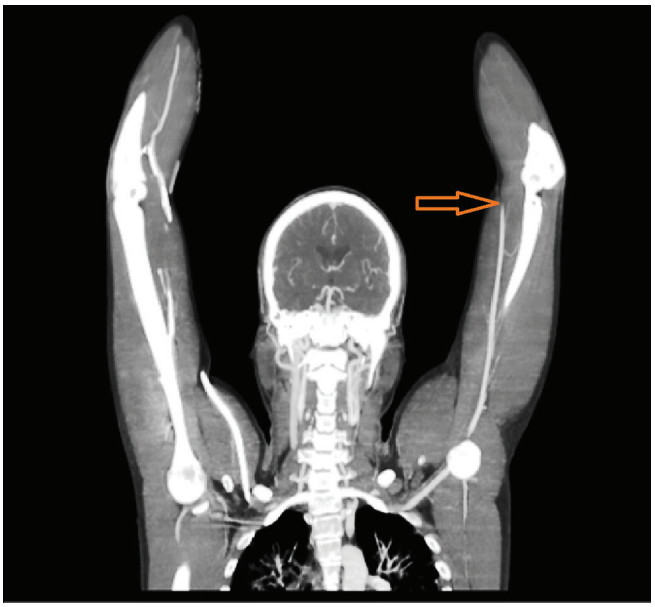

Figure 3: CT angiogram of patient with signs of acro-ischemia showing abrupt cutoff of distal left brachial artery, beginning approximately 3.5 proximal to the elbow joint

No patient from the above set had changes suggestive of COVID-19 on the chest radiograph.

One patient (16.7%) who had changes of acro-ischemia was admitted in ICU, whereas the rest of the patients (83.3%) were admitted in ward.

All above patients were discharged after treatment of COVID-19 and adverse outcomes were not reported in any of them.

On statistical analysis, it was observed that except CRP all variables followed normal distribution pattern. The difference between groups of patients with skin manifestations and those without was not statistically significant for parameters like temperature, SpO_2, hemoglobin, total leucocyte counts, neutrophil count, platelets, CRP levels ($P > 0.05$) [Tables 3 and 4].

The difference in lymphocyte counts between two groups was found statistically significant ($P < 0.05$). The patients without skin manifestations had comparatively lower lymphocyte counts than those with skin manifestations.

Besides these six patients we also came across two patients which were associated indirectly with COVID-19.

One patient, 34-year-old man developed urticaria secondary to administration of favipiravir for COVID-19.

Another patient a 30-year-old man developed papulopustular lesions on back shortly after discharge. The lesions were suggestive of acneiform eruption and records had documentation of receiving parenteral corticosteroids during the hospital stay. Hence the

Table 3: Statistical analysis of parameters following normal distribution by independent *t* test

Parameter	Skin problem	*N*	Mean	SD	*t* Value	*P* Value
Temperature (°F)	Yes	6	97.58	1.88	0.1600	0.87
	No	296	97.46	1.23		
SpO_2	Yes	6	97.67	1.37	0.1360	0.89
	No	296	97.59	2.15		
Hemoglobin (g/dL)	Yes	6	13.95	0.93	2.1800	0.71
	No	268	13.08	2.00		
Total leucocyte count	Yes	6	7433.33	2377.95	1.2300	0.27
	No	266	6222.74	2165.61		
Neutrophil count	Yes	6	70.50	13.34	1.9700	0.103
	No	267	59.64	12.41		
Lymphocyte count	Yes	6	19.17	11.65	2.5500	0.011
	No	267	31.30	11.52		
Platelet count	Yes	6	269500.00	111878.06	0.59	0.58
	No	262	242526.72	83087.48		

Difference between group of patients with skin manifestations and those without skin manifestations was not statistically significant for temperature, SpO2, hemoglobin, total leucocyte count, neutrophil count, and platelets count. The difference was statistically significant for lymphocyte count among two groups

Table 4: CRP levels did not follow normal distribution pattern and was analyzed by Mann–Whitney *U* test

Parameter	Skin problem	*N*	Median	*P* Value
CRP	Yes	6	22.71	0.92
	No	269	19.73	
	Total	275		

Difference between the group with cutaneous manifestations and those without was not statistically significant

diagnosis of steroid-induced acneiform eruption was confirmed.

Discussion

In the initial days of the current pandemic main focus of health care providers was on respiratory system involvement as patient symptoms were predominantly that of respiratory in nature. It was evident from a study in China, which reported 67.8% of subjects had complaints of cough, whereas 18.7% complained shortness of breath.[10]

However as pandemic progressed newer facets emerged regarding multisystem involvement in COVID-19.[9] Naturally, dermatologists also started to try and look for any aspect of disease process which involved skin so as to do our bit in dealing and helping our colleagues on the frontlines of this battle.

This was manifest in the publications of many case reports and few studies which tried to establish useful leads of COVID-19 and skin.[4-7] Many of these links are awaiting evaluation to determine causality.

The picture is still not complete owing to the difficulties regarding quarantines, difficulty in accessing dermatology opinion, lack of awareness among general public (especially in country like India), difficulty in collecting data due to patient isolations and possibility of not reporting minor skin manifestations even by healthcare workers owing to overwhelming burdens on public health care systems.

We also encountered these problems because of limited access to patients as there was fear of contracting infection during interaction with patients.

During the conduct of this study we found that like other viral infections COVID-19 also has cutaneous manifestations.

Incidence of cutaneous rash during COVID-19 in this study was 1.98%.

Some of the initial reports about COVID-19 which were published by authors in China reported the incidence of cutaneous rash as a mere 0.2%.[10] In a study from Spain by Herrero-Moyano *et al.*,[11] the authors reported the incidence of cutaneous manifestations among hospitalized patients with COVID-19 as 0.7%. A study from Italy by Recalcati[4] reported that 20.4% of patients developed cutaneous manifestations. There is only one published study from India regarding cutaneous findings in COVID-19 by Dalal *et al.*[8] In this study 1.9% of patients had urticarial lesions, 2.9% of patients had maculopapular rash, and 7.8% of patients had complaints of pruritus without any signs. In total, 12.7% of patients had cutaneous symptoms during COVID-19.

In this study, we only included the patients who developed demonstrable cutaneous sign and excluded patients who did not have relevant signs and symptoms.

In general, all studies have indicated that COVID-19 has a cutaneous component; however, the incidence of cutaneous manifestations remains a contested point. In general majority of studies have shown low incidence.

In course of this study, we encountered four types of skin lesions- urticaria, maculopapular rash, acral ischemia, and glossitis.

Total four patients developed urticaria during the course of disease. One patient of them was suspected to have developed urticaria secondary to administration of favipiravir. Rest three patients however had no other attributable cause aside from SARS-CoV-2 infection.

Urticaria was the most common cutaneous manifestation among patients with COVID-19 in our study. All patients promptly responded to course of oral antihistamines.

One patient developed maculopapular rash on day 1 of fever. The rash was mildly erythematous and resolved within 24 h with oral antihistamines.

Drug rash should be considered an important differential diagnosis when patients with COVID-19 develop urticarial lesions, maculopapular rash. A proper history taking about drug intake and timing of onset of rash can help to rule out drug rash.

We encountered one patient with findings of acro-ischemia. Multiple authors have reported this finding across the world; however, we are yet to come across report of such finding from India. To the best of our knowledge, this might be the first reported case of such type from India.

Besides the above-reported case we also came across another similar case at our institute where a 35-year-old male patient with COVID-19 developed complaints of cyanosis and pain in the left upper limb. On computed tomography (CT) angiogram examination patient was diagnosed with left brachial and subclavian artery thrombosis [Figures 3 and 4]. D-dimer and CRP levels were also found to be raised. The patient had to be operated to restore blood flow. When this patient presented to us, we had already finished compilation of data and statistical analysis. So unfortunately, his data could not be included in the study. However, we decided to discuss this case in the manuscript to point out the importance of acro-ischemia in patients with COVID-19.

From our experience signs of acro-ischemia can be considered as characteristic cutaneous feature of COVID-19 and can be used to suspect/monitor COVID-19.

This presentation of acro-ischemia is proposed to be due to SARS-CoV-2 induced coagulopathy which culminates in thrombotic events.[12] This coagulopathy is a prominent feature of COVID-19 and presence of coagulopathy has been associated with poor prognosis.[12,13]

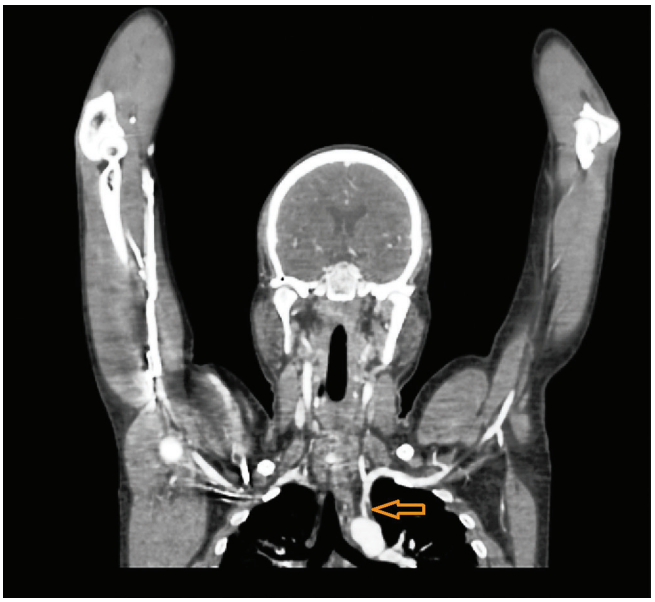

Figure 4: CT angiogram of patient with signs of acro-ischemia showing eccentric partial thrombus in the origin of left subclavian artery

In our study, we came across a patient of glossitis. However, we are of opinion that association of this finding cannot be linked to COVID-19 firmly and could be an incidental finding.

Casas *et al*.[5] published a major study outlining cutaneous manifestations from Spain. In the study, authors developed consensus on five clinical types of rash associated with SARS-CoV-2 infection (Pseudo chilblain, vesicular, urticarial, maculopapular, and necrotic).

We did not encounter any patient with pseudo chilblain and vesicular types of rash.

Vesicular rash has however been reported by multiple other studies in context of COVID-19.[4-6] A study by Fernandez-Nieto[14] carried out polymerase chain reaction on the fluid obtained from vesicles in patients with COVID-19. However, PCR assays failed to detect the presence of SARS-CoV-2 inside the vesicles.

As for pseudo-chillblain the evidence is not yet conclusive. According to two recent studies published concluded that there was no microbiological and serological evidence to implicate SARS-CoV-2 in causation of chilblain-like or perniotic lesions.[15,16] However, another study has suggested that chilblain-like lesions are associated with mild or asymptomatic SARS-CoV-2 infection.[17]

We are of opinion that this needs to be further investigated to draw final conclusions.

These differences in clinical presentation may be due to genetic and ethnic differences among patients.

A statistically significant difference between lymphocyte counts in groups of patients with and without cutaneous manifestations was observed. Further clinical studies may shed light on clinical relevance and impact of this finding.

Collection of data from single center, relatively lower number of patients, and absence of histopathological examination can be considered as limitations of the study. This can be remedied by conducting large study involving multiple centers.

Conclusion

COVID-19 disease process has a cutaneous component; however, the incidence of cutaneous signs in COVID-19 remains low.

Urticaria is the most common cutaneous manifestation of infection with SARS-CoV-2. Other cutaneous manifestations are maculopapular exanthem and acro-ischemia.

Presence of urticarial lesions, maculopapular rash, or signs of acro-ischemia in appropriate clinical settings should alert the dermatologist regarding the possibility of infection with SARS-CoV-2.

Signs of acro-ischemia can be considered as a characteristic cutaneous manifestation of COVID-19.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Dental Patch Test Results and Clinical Relevance: 10 Years of Retrospective Experience

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Abstract

Background: Patch testing with dental screening series [dental patch test (DPT)] is used to detect triggers for mucositis and/or oral lichen planus as well as to detect contact sensitization due to substances and restorative materials used mostly in dentistry. **Aim:** We aimed to retrospectively evaluate the DPT results performed in our clinic in the last 10 years and to assess their clinical relevance. **Methods:** Data of 127 patients who had DPT in our allergy unit between January 2010 and July 2020 were included in our study. In our clinic, DPTs were applied to patients mostly when they have history of metal allergies, oral lichen planus especially close to dental materials, chronic mucositis, and history of allergy after dental procedures. The forms routinely used in our allergy unit were examined retrospectively. **Results:** The most common five allergens were nickel (II) sulfate hexahydrate (29.9%), palladium chloride (18.9%), sodium tetrachloropalladate (II) hydrate (18.9%), gold (I) sodium thiosulfate dihydrate (12.6%), and mercury (10.2%). Fifty-eight of 71 patients with positive PT had a current relevance according to the COADEX coding system ($P < 0.05$). Of the 38 individuals with nickel sensitization, 36 were females and 2 were males, and this result was statistically significant ($P = 0.034$). **Conclusion:** Nickel, palladium, sodium tetrachloropalladate, gold, and mercury, which are frequently found in dental prosthesis and materials, were the most common allergens in our study and this is in accordance with the literature.

Keywords: COADEX, dental serial patch test, mucositis, oral lichen planus

Introduction

Allergic contact dermatitis (ACD) is a delayed type (type IV) hypersensitivity reaction caused by substances in contact with the skin in previously sensitive individuals. Patch test (PT) is the most important diagnostic method to confirm the diagnosis of ACD, and it enables us to find the cause of contact allergy.[1] European Standard Serial Patch Tests (ESS PTs) were created by bringing together the most common contact allergens in daily life. Generally, only 80% of common allergens can be detected with ESS PT.[2] Due to the need for different allergen series for the detection of specific allergens, besides the standard series, other special patch test series (dental, cosmetic, medicine, etc.) compatible with the patient's profession, location of dermatitis, and/or clinical findings are also used. Patch testing with dental screening series [dental patch test (DPT)] is used to detect triggers for mucositis and/or oral lichen planus as well as to detect contact sensitization due to substances and restorative materials used mostly in dentistry.[3,4]

In our study, we aimed to retrospectively evaluate the DPT results performed in our clinic in the last 10 years and to assess their clinical relevance.

Materials and Methods

Data of 127 patients who had DPT in our allergy unit between January 2010 and July 2020 were included in our study. In our clinic, DPTs were applied to patients mostly when they have history of metal allergies, oral lichen planus especially close to dental materials, chronic mucositis, and history of allergy after dental procedures.

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The forms routinely used in our allergy unit were examined retrospectively, and the sociodemographic data of the patients, history of atopy, accompanying diseases, DPT results, and clinical relevance evaluated with the COADEX coding system were analyzed.[5-8] Patients with positive reactions in DPT were also tested with the relevant materials provided by their dentists as pure metal plaques and/or ready-to-use material. Our study was approved by the Faculty of Medicine, Akdeniz University, Clinical Research Ethics Committee (70904504/461).

Application of DPT: Patients who underwent DPT were not receiving topical steroid treatment for at least 1 week and systemic steroids for 2 weeks before the DPT. The DPT materials routinely used in our allergy unit are allergens imported from Chemo Technique Diagnostic (Malmo, Sweden), and their names and locations are shown in Table 1. The IQ Chambers unit consisting of 10 small squares of 9 × 9 mm size made of plastic was used to apply the test substances to the skin. The upper back of the patient was used as the test area. DPTs were duly done, and positive reactions were interpreted by a doctor with sufficient experience and were classified according to the criteria of the International Contact Dermatitis Working Group (ICDWG).[1] The DPT was considered positive if at least 1+ reaction was detected against any substance.

Data were evaluated statistically by using SPSS for Windows version 23.0 software program. Measurable variables were presented as mean ± standard deviation, and categorical variables as numbers and percentages. Pearson's χ^2 and Fisher's exact χ^2 test, among other statistical methods, were used. $P < 0.05$ was considered statistically significant.

Results

In our study, a total of 127 patients [107 (84.3%) were females and 20 (15.7%) were males] who underwent DPT between January 2010 and July 2020 were identified. The average age was 51.3 ± 12.92 (age range 7–81) years. The mean duration of complaints was 47.35 ± 81.03 months. Forty patients (31.5%) had a history of personal atopy, 23 (18.1%) had a history of familial atopy, and 52 (40.9%) had a history of known contact dermatitis. The most common five allergens were nickel (II) sulfate hexahydrate (29.9%), palladium chloride (18.9%), sodium tetrachloropalladate (II) hydrate (18.9%), gold (I) sodium thiosulfate dihydrate (12.6%), and mercury (10.2%) [Table 2].

Fifty-eight of 71 patients with positive DPT had a current relevance according to the COADEX coding system ($P < 0.05$) [Table 3]. Out of the 38 individuals with nickel sensitization, 36 were females and 2 were males, and this result was statistically significant ($P = 0.034$). Mercury and palladium chloride sensitization were significantly more frequent in patients with a known history of contact dermatitis ($P = 0.029$ and $P = 0.004$, respectively). No relationship was observed in terms of personal atopy, familial atopy, presence of accompanying autoimmune diseases, hobbies, or professions with any allergen sensitivity. Most of the patients were housewives ($n = 79$, 62.2%). The professions of the individuals in our study are shown in Table 4.

In our study, a significant relationship was found between all five most frequently detected allergens and their current relevance according to the COADEX coding system ($P < 0.05$). COADEX coding results are shown in Table 3. None of the 127 patients had an allergic reaction to camphor quinone, caruon, methacryloxyetoxyphenil, drometrizole, and glutaral.

Discussion

Contact dermatitis and sensitization (mucositis or stomatitis) of the oral mucosa are relatively rare. As the oral mucosa is constantly washed with saliva, the sensitizers are continuously cleared from the mucosal surface and prolonged contact is prevented. The dense vascular structure of the mucosa also provides quick cleansing and rapid absorption of the allergen.[9,10] Allergic reactions or sensitization in the oral mucosa may represent with different symptoms and signs such as erythematous, erosive, lichenoid, hypertrophic stomatitis/lesions, and/or burning mouth.

The most important allergens are basically metals used in dental treatment and dental prosthesis materials. Apart from these, mouthwashes, toothpastes, chewing gum or aromatic fragrances in foods and beverages, cinnamon, mint flavorings, preservatives, antiseptics, antibiotics, active ingredients, or formulations of topically used medications (mouthwash, sprays, gels) can also cause allergic contact sensitization in the oral mucosa.[9,10]

In our study, nickel, palladium, sodium tetrachloropalladate, gold, and mercury, which are often found in dental prostheses and materials, were the most common allergens consistent with the literature.[9-15] The most common allergen was determined to be nickel (II) sulfate hexahydrate. Nickel is found in many areas of daily life such as materials (metal buttons, zippers, metal and shoe paints, spectacle frames, etc.); it is also found in dental prostheses. Although nickel has a high potential for allergy, the risk of allergy formation of high-quality dental nickel–chromium alloys is less than allergy due to food or booger.[16,17] It is recommended to use only alloys with a chromium or molybdenum content above 20% in nickel–chromium alloys, as this ratio is necessary for resistance to corrosion. As the ion release of corrosion-resistant alloys is lower, nickel in these alloys is not expected to cause contact sensitization.[16,18] However, if the person has a nickel allergy, it is recommended to completely avoid the use of nickel–chromium alloys in dental materials and prostheses. Palladium chloride, which is the second most common allergen in our study, is used especially in dental metal alloys,

Table 1: Dental serial patch test materials and areas of use (https://www.chemotechnique.se/)

Dental materials—components	Area of use
1. Methyl methacrylate	A methacrylic monomer in plastics for dentures, bone cement, artificial nails, hearing aids, etc.
2. Triethylene glycol dimethacrylate	A methacrylic monomer used as cross-linking agent for adhesives and dental restorative materials.
3. Urethane dimethacrylate	A methacrylate based on a methacrylate aliphatic isocyanate. Used in dental bonding agents, resin veneering, and restorative materials
4. Ethylene glycol dimethacrylate	A cross-linking methacrylic monomer in dental composites, sealants, prostheses, adhesives, artificial nails, etc.
5. Bisphenol A glycerolate dimethacrylate	Common methacrylic monomer in dental composite restorative materials and dental sealants.
6. N,N-dimethyl-4-toluidine	An amine accelerator for the polymerization of e.g., dental methacrylic restorative materials.
7. Benzophenone-3	Common UV-adsorber in dental composite materials and other plastic materials. Used as a UV-adsorber in topical sunscreens, lipsticks, lip balms, nail polish, etc.
8. 1,4-Butanediol dimethacrylate	A cross-linking methacrylic monomer for use in dental composite materials, sealants, prostheses, etc.
9. Bisphenol A dimethacrylate (BIS-MA)	Methacrylic monomer based on bisphenol A. Used in dental restorative composite and adhesive materials.
10. Potassium dichromate	This hapten is a marker for contact allergy to chromium.
11. Mercury	Is a chemical reagent and can be found in thermometers and dental amalgam, but also in pharmaceuticals, antifouling paints, agricultural chemicals.
12. Cobalt (II) chloride hexahydrate	This hapten is a marker for contact allergy to cobalt. Used in various alloys (dental, etc.).
13. 2-Hydroxyethyl methacrylate	A methacrylic monomer used in UV-inks, adhesives, lacquers, dental materials, artificial nails, etc.
14. Gold(I) sodium thiosulfate dihydrate	A gold derivative used for screening of contact allergy to dental gold materials.
15. Nickel (II) sulfate hexahydrate	Nickel metal: a common hapten present in nickel plating for alloys, dentures, orthopedic plates, spectacle frames, etc.
16. Eugenol	Used as fragrance in perfumery as substitute for oil of cloves. Dental analgesic in impression materials and periodontal packings.
17. Colophonium	A yellow resin used as a component in dental impression materials and periodontal packings (rosin).
18. N-Ethyl-p-toluene sulfonamide	A resin carrier found in dental materials used for isolating cavities below restorations.
19. Formaldehyde	Used in the production of urea, phenolic melamine, and acetate resins. Used as anti-cracking agent in dental plastics.
20. 4-Tolyldiethanolamine	An amine accelerator for the polymerization of, e.g., dental acrylic composite restorative materials.
21. Copper (II) sulfate pentahydrate	This hapten is a marker for contact allergy to copper. Copper metal is used in, e.g., dental alloys.
22. Methyl hydroquinone	A stabilizer and antioxidant in acrylic monomers to prevent polymerization.
23. Palladium (II) chloride	This hapten is a marker for contact allergy to palladium. A chemical catalyst. Can be found in dental alloys.
24. Aluminum (III) chloride hexahydrate	This hapten is a marker for contact allergy to aluminum. Found in dental ceramics and topical astringents.
25. Camphor quinone-Bornane dione	An initiator for visible light-cured dental acrylic composite materials.
26. Dimethyl aminoethyl methacrylate	Used as amine activator in visible light-cured dental acrylic composite materials.
27. 1,6-Hexanediol diacrylate	A common acrylic monomer in dental composite materials.
28. Drometrizole	A UV-adsorber used in plastics, cosmetics, dental materials, acrylic materials, dyes, etc.
29. Tetrahydrofurfuryl methacrylate	A methacrylic component used in dental materials such as crown and bridge products. Also used as a component in artificial nails.
30. Tin	Metal used in tin plating, soldering and dental alloys, collapsible tubes.
31. Sodium tetrachloropalladate (II) hydrate	This hapten is a marker for contact allergy to palladium. It is an inorganic compound used in among other things in chemical synthesis as a catalyst. It is present in many alloys containing palladium.
32. Carvone %5.0	Found in several essential oils and is used for flavoring liqueurs, soaps, dental materials, and perfumes.
33. 2,2-bis(4-(2-methacryl-oxyeth-oxy)phenyl)	A methacrylic monomer based on bisphenol A. Used in dental restorative composite materials and as a reactive monomer in adhesive products.
34. Glutaral %0.2	Used in the sterilization of endoscopic instruments, dental, and barber equipment. Also known as glutaraldehyde.

electronics, medicine, and electroplating in jewelery. The incidence of palladium allergy is controversial. It is claimed that people with nickel allergy may often develop allergic reactions to the palladium.[19] Sodium tetrachloropalladate (II) hydrate is the third most common in our series. It is suggested that patch testing with this material is more useful in detecting palladium contact sensitization than testing with palladium chloride.

Other common allergens in our study were gold (I) sodium thiosulfate dihydrate, which is a gold material in dental prothesis, and mercury, which is a chemically reactive agent and is used in pharmacology, thermometers, the chemical industry, and dental amalgams. The degree of allergic potential of gold is controversial, and it is claimed that allergic reactions developed due to some irregularities in test materials. In the last decades, gold alloys are considered as rare allergens in the medical field.[20] Mercury and mercury compounds are the most common causes of amalgam-mediated allergy, and other metals in amalgam content are rarely blamed for amalgam sensitization. Dental amalgam is the restoration material that has been used in routine filling in dentistry since the beginning of the last century. It is formed by mixing metal powders such as silver (Ag), copper (Cu), zinc (Zn), tin (Sn) with mercury (Hg).[14,21,22] Three different reactions have been described, namely, type 4 hypersensitivity, toxic reaction, acute or generalized hypersensitivity associated with amalgam.[20,22,23] The most common reaction due to amalgam is lichenoid-type contact stomatitis that develops in the vicinity of amalgam.[23,24] In the studies conducted, it has been found that there is a strong anatomical proximity between the filling and the lesion in 70% of the patients with a positive reaction due to amalgam. DPT should be especially considered in the presence of treatment-resistant lichen planus or mucositis, lesions adjacent to the dental materials, and asymmetrical distribution.[21,24] Toxic reactions are associated with the direct contact of amalgam filling and its components to the oral mucosa for years. It also occurs frequently in fillings with high zinc content. Toxic reactions and the clinical findings resulting from type 4 hypersensitivity reaction cannot be distinguished from each other. However, it is thought that the negative result of DPT can be interpreted in favor of a toxic reaction.[21]

Apart from this, hypertrophic allergic contact stomatitis can also occur with other metals with frequent sensitivity (nickel, palladium, gold, copper, and cobalt).[3,14] Due to the retrospective nature of our study, we could not make a clear interpretation between the allergens we detected and the clinical type of stomatitis in the mucosa, as detailed clinical examination of the oral mucosa of patients could not be reached from patient files.

In our unit, especially in patients who were consulted by the dentists for allergic sensitivity to dental prostheses and materials, the metal content of existing dental materials was determined or metal plate samples belonging to these materials were obtained from dentistry, and DPT was tested along with these materials. This application enabled the appropriate evaluation according to the COADEX coding system and the current relevance with the five most common allergens was found to be statistically significant. In cases diagnosed with ACD and/or stomatitis, not

Table 2: The most common five allergens

Allergens	Patients, *n* (%)
Nickel (II) sulfate hexahydrate	37 (29.9)
Palladium chloride	24 (18.9)
Sodium tetrachloropalladate (II) hydrate	24 (18.9)
Gold (I) sodium thiosulfate dihydrate	16 (12.6)
Mercury	13 (10.2)

Table 3: Results of the COADEX coding system for assessing clinical relevance

COADEX coding system	Patients, *n* (%)
Current relevance (the patient has been exposed to allergen prior to the current episode of dermatitis and improves when the exposure ceases)	58 (45.7)
Old/past relevance (past episode of dermatitis from exposure to allergen but not encountered before present relapse)	2 (1.6)
Exposed (a history of previous exposure but not resulting in dermatitis from that exposure)	7 (5.5)
Doubtful relevance (relevance difficult to assess, no traceable relationship between the positive test and the disease)	4 (3.1)
Negative (no reaction detected)	56 (44.1)

Table 4: Professions of patients who underwent dental serial patch test

Profession	Patients, *n* (%)
Housewife	79 (62.2)
Other (social occupations, shop, market, etc.)	17 (13.4)
Office work	6 (4.7)
Scientific-academic (engineering, lawyer, teaching, psychologist, journalism, journalism)	5 (3.9)
Metal worker, turner, jeweler	5 (3.9)
Farmer	5 (3.9)
Health worker (dentist, doctor, nurse, veterinarian, etc.)	4 (3.1)
Chef, baker	3 (2.4)
Student	2 (1.6)
Carpenter	1 (0.8)

only performing PT to determine the cause, but more importantly revealing the relationship of PT results and clinical relevance is one of the most important steps. For this purpose, the use of standardized evaluation methods is very important because it allows more accurate interpretation of test results, better statistical comparisons via using common evaluation criteria in studies, and determination of the true relationship between allergens and clinical findings.

Considering contact with dental materials, if a positive reaction is detected in the DPT, the responsible dental metal and materials must be removed, and oral lesions are expected to regress after the removal of the responsible material. The DPT is not a 100% reliable test, and false positive reactions have been reported, albeit at a low rate (3.2%).[9] Therefore, positive reactions should be evaluated using the COADEX coding system. Thus, determining the relationship between the clinical findings and allergens will guide the intervention and treatment attempts to be made after the PT.

Due to the retrospective nature of our study, the number of patients included in the analysis was relatively low. Other limitations were insufficient information about the mucosal clinical findings (stomatitis, lichen planus, etc.) obtained from the files, being without a control group, and the follow-up information of all patients could not be reached during the follow-up.

The results of DPT performed in our clinic were found to be compatible with the current literature. DPT, which is a non-invasive and practical method, is useful to identify the contact allergy of dental restoration before any procedures are planned if there is a suspicion of contact allergy.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

The Effect of Omalizumab Treatment on Hematological Inflammatory Parameters and Immunoglobulin E Levels in Patients with Chronic Spontaneous Urticaria

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Abstract

Objectives: We aimed to evaluate the effect of omalizumab use on hematological parameters, inflammatory markers, and immunoglobulin E (IgE) in patients with chronic spontaneous urticaria and to determine whether there would be any difference between patient and control groups in terms of these values and whether IgE levels before and after omalizumab treatment are correlated with the Urticaria Control Test (UCT). **Materials And Methods:** Forty-five patients with chronic spontaneous urticaria and 45 healthy controls who presented to the dermatology outpatient clinic of Yozgat Bozok University Research and Training Hospital were analyzed retrospectively. Age, gender, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and thrombocyte counts and IgE values before and after 24 weeks of treatment were recorded, and IgE ratios before and after treatment were calculated. The UCT was performed on the patients. The neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, eosinophil/basophil, and eosinophil/lymphocyte ratios were calculated for the control group and the patient group, both before and after treatment. Mean platelet volume (MPV), which is also considered an inflammatory marker, was recorded before treatment, in both the control group and the patient group. **Results:** The patients' median pre-treatment IgE level [189.0 (1.0–1824.0)] was significantly lower than the post-treatment level [561.0 (2.0–4301.0)] (P<0.001). No significant difference was determined in basophil, platelet, eosinophil, monocyte, lymphocyte, and neutrophil counts and neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, eosinophil/basophil, and eosinophil/lymphocyte ratios before and after omalizumab treatment. The mean UCT score of the patients was found to be 11.5 (± 3.9). The mean IgE ratio post-omalizumab treatment/pre-omalizumab treatment was 5.8. No significant difference was found between the patient and control groups regarding neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, eosinophil/basophil, and eosinophil/lymphocyte ratios, as well as MPVs. A significant correlation was found between the patients' UCT scores and IgE levels after omalizumab treatment (r=0.313; P=0.046). **Conclusion:** No changes were observed in hematological inflammatory markers of patients with chronic spontaneous urticaria, compared with healthy controls. Besides, no changes were observed in either inflammatory markers or hematological parameters, following the use of omalizumab in these patients. Hence, it is considered that there is no harm in using omalizumab in diseases such as chronic disease anemia, chronic idiopathic neutropenia, and idiopathic thrombocytopenic purpura. The fact that omalizumab treatment caused a significant increase in IgE levels, in correlation with previous studies, made us think that the methods of reducing the dose or extending the dose interval should be preferred, instead of abruptly interrupting the treatment during the discontinuation period to prevent relapses.

Keywords: Blood cell count, chronic urticaria, immunoglobulin E, inflammation mediators, omalizumab

Introduction

Urticaria is a disease that can be seen in 15–25% of individuals in society at some point in their life and is

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common in the routine of dermatology outpatient clinics. Urticarial lesions can occur anywhere on the body and are characterized by lesions that itch, redden, swell, and disappear as described classically. Lesions lasting less than 6 weeks are called "acute," whereas lasting longer than 6 weeks are called "chronic" urticaria. The chronic urticaria disease is also divided into two: "chronic spontaneous urticaria (CSU)" and "chronic inducible urticaria."[1]

Various mechanisms such as autoimmunity, chronic infections, stress, pseudoallergens, and autoinflammation are emphasized in the pathogenesis of CSU. C-reactive protein (CRP) is a sensitive marker of inflammation and has been found to be high in chronic urticaria.[2] Therewithal, studies have shown that CRP elevation is associated with urticaria disease activity.[2,3] Following these studies, investigations of inflammation markers have gained momentum to elucidate the pathogenesis of CSU. Platelet count, mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), eosinophil/basophil ratio (EBR), eosinophil/lymphocyte ratio (ELR), and platelet/lymphocyte ratio (PLR) are among these inflammatory markers and can be easily obtained from a complete blood count with a low cost. In some of the studies conducted so far, it has been evaluated whether there is a difference in these values between the patient and control groups and whether there is a change before and after treatment with omalizumab, a monoclonal antibody used in the treatment of CSU.[4-7] The results of these studies differ from each other. With the widespread use of omalizumab in the treatment of chronic urticaria, studies have focussed on the fact that pre-treatment immunoglobulin E (IgE) level can be used as a criterion for predicting response to omalizumab treatment, and IgE increased coefficient during treatment may be related to Urticaria Control Test (UCT) scores.[8-10] In recent years, the UCT has been developed, in the evaluation of chronic urticaria activity, as it can both promote patient adherence and can be used practically in the daily outpatient clinic routine.[11] The use of UCT has played a role in guiding the physician and in deciding to continue or alter treatment in follow-up and facilitated the evaluation of disease activity in studies with CSU.

In line with this information, we intend to assess the impact of omalizumab use on hematological parameters, inflammatory markers, and IgE in patients with CSU. However, it was investigated whether there was a difference between the patient and control groups in terms of these values, and the correlation between post-treatment IgE/pre-treatment IgE ratios and UCT.

Materials and methods

The study protocol was approved by the Yozgat Bozok University Ethics Committee [2017-KAEK-189_2021.01.18_10]. Forty-five CSU patients, treated with omalizumab, and 45 controls, age- and gender-matched, examined for routine health check-ups, and had no systemic disease or smoking, were included in the study. The study was performed with the patients who applied to the Yozgat Bozok University Research and Training Hospital Dermatology Outpatient Clinic from June 2016 to December 2020. The data were obtained retrospectively from the hospital registry system. Patients with hemogram values and IgE values, before and after 24 weeks of omalizumab treatment, were included in the study. Patients with missing hospital registration information, any comorbidity of inflammatory systemic disease, and smokers were excluded from the study. Age, gender, neutrophil, lymphocyte, monocyte, eosinophil, basophil, thrombocyte counts, and IgE values before and after 24 weeks of treatment were recorded, and post-treatment IgE/pre-treatment IgE ratios were calculated. UCT was performed on the patients. NLR, PLR, LMR, EBR, and ELR values of the patient group were calculated, before and after the treatment, and also the same values of the control group were calculated. Moreover, pre-treatment values of MPV, which is also considered an inflammatory marker, were recorded in both the control group and the patient group.

Statistical analysis

In summarizing data from the study, descriptive statistics are tabulated for continuous (numeric) variables as mean ± standard deviation or median, minimum, and maximum, depending on the distribution. Categorical variables were outlined as numbers and percentages.

The distribution normality of numerical variables was analyzed via Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests. In the comparison of two independent groups, a *t*-test was used for independent groups when numerical variables conformed to a normal distribution, and the Mann–Whitney *U*-test was used when they did not show normal distribution. In the comparison of some clinical parameters before and after treatment, the *t*-test was used for dependent groups in cases in which the variables were normally distributed, and the Wilcoxon test was used when they did not. Spearman's rho correlation coefficient was used to analyze the correlations between UCT and IgE values, before and after omalizumab treatment. Statistical analyses were performed using the software of the Jamovi project (2020), Jamovi (Version 1.8.1) (Computer Software) (retrieved from https://www.jamovi.org) and JASP (Version 0.14.1.0) (retrieved from https://jasp-stats.org), and the level of significance was considered as 0.05 (*P*-value).

Results

The mean age of the patients was 43.9 (±14.7). Thirty (66.7 %) patients were female, and 15 (33.3 %) were male.

The mean UCT score of the patients was found to be 11.5 (± 3.9). Mean IgE ratios of patients post-omalizumab/pre-omalizumab treatment was 5.8 [Table 1].

The median IgE level of the patients before treatment [189.0 (1.0−1824.0)] was significantly lower when compared with the post-treatment level [561.0 (2.0−4301.0)] (P<0.001). No significant difference was found, between pre-treatment and post-treatment basophil, platelet, eosinophil, monocyte, lymphocyte, neutrophil, NLR, PLR, EBR, LMR, and ELR levels [Table 2 and Figure 1]. No significant difference was determined between the NLR, PLR, EBR, LMR, ELR, and MPV values of the patient and control groups [Table 3].

A significant positive correlation was found between UCT scores of the patients and their IgE levels post-omalizumab treatment (r=0.313; P=0.046). However, no correlation was determined between the UCT scores of the patients and IgE levels pre-omalizumab treatment [Table 4 and Figure 2].

Discussion

CSU is a disease with attacks of itching, redness, swelling, and disappearance. Patients often experience these attacks, that last longer than 1 year, and in a substantial proportion, CSU persists for 5 years or more. These attacks cause problems such as sleep disorders, emotional stress, and loss of work in patients and lead to an increase in the current vicious cycle of the disease and a severe deterioration in the quality of life.[12,13] CSU remains idiopathic, with a high rate of 45% even after 10 years of follow-up; however, various autoimmune diseases, chronic infections, and immune disorders may occur through the duration of the disease in some patients.[13] Therefore, studies on this idiopathic group are still ongoing.

The aim of treatment in CSU is to improve the quality of life and to ensure the continuity of the treatment by preferring treatments with a low adverse effect profile as it is a chronic disease. In up-to-date treatment guidelines, the use of antihistamine medications is recommended as the first-line treatment. Of these agents, non-sedating, second-generation antihistamines should be preferred, and the dose should be increased up to four times a day, depending on the treatment response. Nonetheless, in some patients, the symptoms may not be controlled with the use of high-dose antihistamines. In this situation, the use of omalizumab, an anti-IgE monoclonal antibody, is recommended as an efficient and safe agent.[14] Through binding to free IgE with high affinity, omalizumab prevents allergen-specific IgE from binding to its specific receptor on the mast cell surface. It has no direct impact on mast cells or basophils, as it does not bind directly to cell surface IgE. Thus, it is not expected that omalizumab treatment alters the number or function of blood cells.[6,15,16] The findings of our study are also in line with this expectation. Compared with pre-treatment levels, no difference was determined in the leukocyte, neutrophil, eosinophil, monocyte, basophil, and platelet counts of patients, after 24 weeks of omalizumab treatment. Because omalizumab has no impact on hematological parameters, it can be used safely in the treatment of patients with hematological comorbidities, such as chronic disease anemia, chronic idiopathic neutropenia, and idiopathic thrombocytopenic purpura. Likewise, in the study of Çildağ and Şentürk,[10] no change was observed in eosinophil, lymphocyte, and platelet counts, following 12 weeks of omalizumab treatment. As stated earlier, a compensatory increase in IgE is expected in the patients using this treatment, as omalizumab binds to free IgE with high affinity. In support of this finding, the mean coefficient of IgE increase, before and after 24 weeks of omalizumab treatment, was found to be 5.8 in the present study. This finding clinically indicates that, even if the disease is under control, the decision to discontinue the treatment should be as controlled as possible, because of the fact that free IgE increases with omalizumab treatment. To prevent disease recurrence, it would be a better choice to either extend the dose intervals or reduce the dose. Similar to our review, in the report of Türk *et al.*,[17] although there are no definitive literature data on this subject yet, based on real-life data, it was recommended to gradually discontinue omalizumab treatment by extending the dose intervals.

Numerous studies have scrutinized the validity of serological tests in CSU, to establish the theory of autoimmune disease and to form an autoimmune basis.

Table 1: Sociodemographic characteristics and laboratory values of the patients

	Mean ± SD/*n* (%)	Median [Min.–Max.]
Age	43.9 ± 14.7	43.0 [18.0–76.0]
Sex (%)		
Male	15 (33.3)	15 (33.3)
Female	30 (66.7)	30 (66.7)
Urticaria Control Test	11.5 ± 3.9	12.0 [0.0–16.0]
"Post-treatment/pre-treatment IgE"	5.8 ± 10.6	3.2 [0.7–68.0]

Descriptive statistics were presented as mean ± standard deviation or median [min-max] depending on distribution for numerical variables and number (%) for categorical variables.

Table 2: Comparison of patients' pre-treatment and post-treatment laboratory parameters

	Pre-treatment	Post-treatment	*P*-value
IgE (ng/mL)	189.0 [1.0–1824.0]	561.0 [2.0–4301.0]	<0.001**
Basophil count	0.0 [0.0–2.0]	0.0 [0.0–2.0]	0.134**
Platelet count	277.0 [136.0–417.0]	269.0 [161.0–453.0]	0.901**
Eosinophil count	0.1 [0.0–1.0]	0.1 [0.0–1.2]	0.540**
Monocyte count	0.5 ± 0.2	0.5 ± 0.1	0.768*
Lymphocyte count	2.4 ± 0.6	2.4 ± 0.7	0.803*
Neutrophil count	4.9 ± 1.9	4.8 ± 1.8	0.744*
NLR	2.1 ± 0.8	2.1 ± 0.8	0.792*
PLR	121.2 ± 45.6	123.6 ± 52.9	0.637*
EBR	3.6 [0.0–100.0]	3.5 [0.0–15.2]	0.528**
LMR	4.9 [2.4–8.8]	4.8 [0.6–80.0]	0.657**
ELR	0.1 [0.0–0.6]	0.1 [0.0–0.7]	0.906**

*The *t*-test was used for dependent groups

**The Wilcoxon test was used

The underlined *P*-values were considered significant ($P<0.05$)

Descriptive statistics were presented as mean ± standard deviation or median [min–max], depending on distribution for numerical variables.

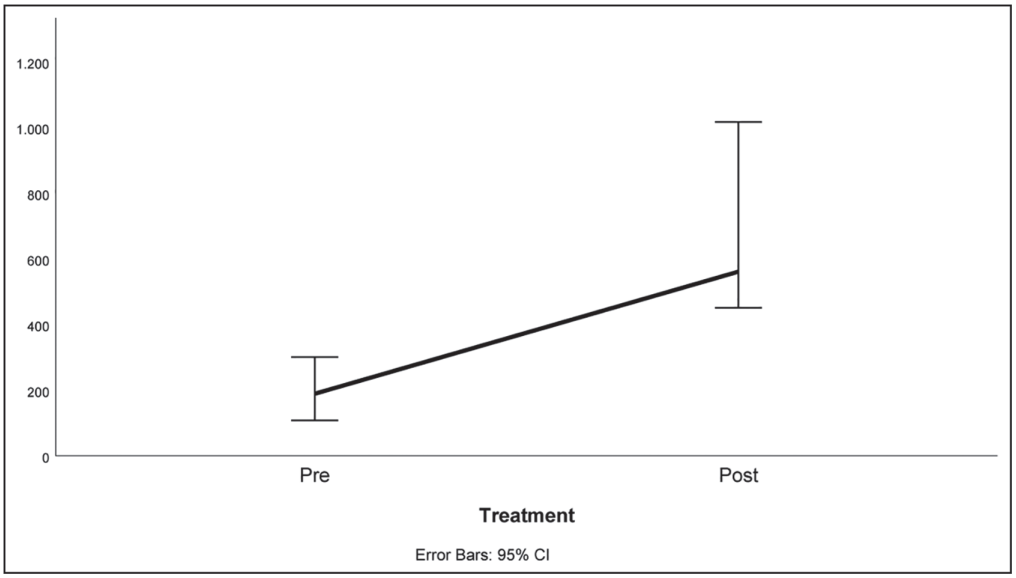

Figure 1: IgE change before and after omalizumab treatment

Immunological changes in the etiopathogenesis of CSU include findings such as increase in the number of T lymphocytes and autoreactive T cells, increase in TNFα, IL-10, MIP-Iα, and RANTES secretion from peripheral blood mononuclear cells, decrease in IL-4 secretion, impaired TLR9-mediated interferon-α production, increased levels of TNF, IL-1β, IL-6, IL-13, IL-12p70, IL-10, IL-31, and B-cell activating factor in serum, as well as increased levels of D-dimer and prothrombin fragments.[18] In the literature, NLR and PLR in various chronic diseases, EBR and ELR in pre-operative and post-operative follow-up in patients with sinonasal polyposis, and LMR in cancer types such as ovarian cancer and gastric cancer as a predictor of poor prognosis have been used. And also LMR has been used as a criterion for response to treatment in the use of some targeted drugs in B-cell lymphoma.[19-24] As the autoimmune hypothesis is emphasized in the pathogenesis of CSU, as mentioned earlier, NLR, PLR, EBR, LMR, and ELR values, which are now considered as inflammatory markers in many diseases, were investigated in the present study. Therefore, the values before and after 24 weeks of omalizumab treatment in the patient group were compared, and it was also assessed whether there was a difference in these values before treatment in the patient group when compared with the control group. The results indicate that there is no difference in hematological inflammatory markers in CSU patients, compared with the control group. This outcome can be interpreted as a supporting finding that the inflammatory process in CSU is mainly dominated by cellular immunity. Moreover, it was observed that the use of omalizumab treatment did not lead to any change in these inflammatory markers. When the other studies in the literature on this subject are reviewed, it

Table 3: Comparison of laboratory values of patient group and control group

	Patient ($n=45$)	Control ($n=45$)	*P*-value
NLR	2.1 ± 0.8	1.9 ± 1.1	0.220
PLR	121.2 ± 45.6	126.7 ± 65.3	0.645
EBR	3.6 [0.0–100.0]	2.5 [0.0–16.5]	0.119
LMR	4.8 ± 1.4	4.5 ± 1.6	0.373
ELR	0.1 [0.0–0.6]	0.0 [0.0–0.2]	0.058
MPV	10.1 ± 0.9	9.9 ± 0.9	0.373

*The *t*-test was used for independent groups

**The Mann–Whitney test was used

Descriptive statistics were presented as mean ± standard deviation or median [min–max], depending on distribution for numerical variables

is noticed that similar to the present study, Ertaş *et al.*[4] found that there was no difference in NLR in the patient group compared with the control group, but unlike our results, NLR decreased after 12 weeks of omalizumab treatment. In the study of Tamer,[6] LMR, PLR, and NLR values were analyzed before and after 12 weeks of omalizumab treatment, and it was revealed that MLR and NLR decreased after treatment, whereas PLR increased; however, this difference was not significant. In the study of Ataseven *et al.*,[25] only NLR and PLR were compared between the patient and control groups regardless of treatment, and similar to our results, no significant difference was detected between them. Besides, in the study of Aktaş Karabay *et al.*,[26] NLR was found to be higher in CSU patients, compared with the control group; other inflammatory markers were not investigated, and their changes after any treatment were not studied. To the best of our knowledge, there is no study in the literature investigating the change in EBR and ELR values before and after treatment in CSU patients or comparing these values with the control group.

In several studies in recent years, similar to hematological inflammatory markers, MPV values were also found to be different in some diseases, compared with control groups, and it was suggested that MPV could be used as an inflammatory marker. For instance, MPV values of patient groups in ankylosing spondylitis, rheumatoid arthritis, and CSU were observed to be lower, compared with the control groups.[4] Contrary to these results, in the present study, no significant difference was determined between patient and control groups in terms of MPV. The difference in studies may be due to the varying number of patients.

When the UCT scores were examined, it was found that the mean score was 11.5, even after a long 24-week treatment period. Yet, if the UCT score is 12 and above, the symptoms of the disease are considered to be under control. This result demonstrates that there are still patients whose symptoms continue, despite using omalizumab treatment. The results of a recent study by Maurer *et al.*[27] support this outcome, and it was found that 27% of CSU patients followed up for 2 years, and using omalizumab treatment,

Table 4: Correlations between pre- and post-treatment UCT and IgE levels of patients

		Spearman's rho	*P*-value
UCT	Pre-treatment—IgE	0.220	0.146
UCT	Post-treatment—IgE	0.313	0.036

Spearman's rho correlation coefficient was used

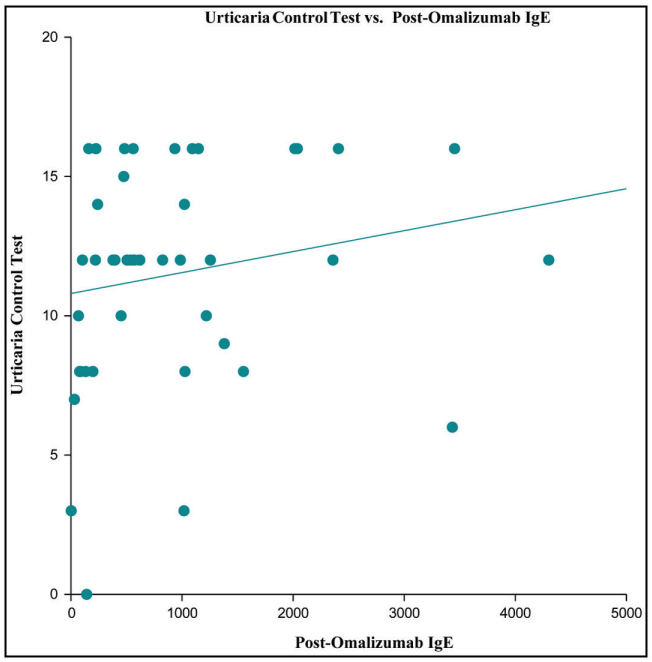

Figure 2: Positive correlation between UCT scores and post-omalizumab treatment IgE levels

had UCT scores below 12 and were "not under adequate treatment." Hence, we should check out the UCT scores, which is a practical measure at each outpatient clinic visit, and consider other treatment options in patients who are not under adequate control. Another remarkable finding in the present study is the positive correlation between UCT and post-omalizumab treatment IgE values. This result reveals that patients with high IgE levels after omalizumab treatment have fewer urticarial symptoms than patients who remain at low IgE levels. Although there is currently no target level related to the IgE level intended to be reached, these data may conduct us in deciding to switch to alternative treatment options more rapidly in a patient who can be mild to moderately controlled with omalizumab treatment. There are numerous studies in the literature that support this finding.[8,9,28] In these studies, therewithal, it has been emphasized that increased total IgE may be associated with higher disease activity, longer disease duration, good response to omalizumab treatment, and rapid relapse after omalizumab treatment discontinued.

Limitations of the study

The study has several limitations. The first of these is that the study was designed retrospectively. For this reason, patients

who did not attend follow-ups or whose blood tests were not performed in some of their follow-ups were excluded from the study, thus the sample size remained small. Consequently, although there is a quantitative difference between the investigated values, this difference may not have been significant. Hence, more valid results can be obtained if a similar study with larger sample size is conducted prospectively. The second limitation is the memory factor that might have occurred due to the computation of the patients' UCT scores at the 24th week of their treatment and the retrospective questioning of the UCT scores before the treatment when attended the follow-up. Thus, the calculation of the current UCT scores of the patients who presented due to CSU at each follow-up would be more helpful in the follow-up of the treatment and would provide more accurate results in terms of scientific studies.

Conclusion

Compared with healthy controls, no changes were observed in hematological inflammatory markers in CSU patients. Moreover, no changes were observed in both inflammatory markers and hematological cell counts due to omalizumab use. Hence, it is considered that there is no harm in using omalizumab in diseases such as chronic disease anemia, chronic idiopathic neutropenia, and idiopathic thrombocytopenic purpura. The fact that omalizumab treatment caused a significant increase in IgE levels, in correlation with previous studies, made us think that the methods of reducing the dose or extending the dose interval should be preferred, instead of abruptly interrupting the treatment during the discontinuation period to prevent relapses. Another remarkable finding in the present study is the positive correlation between UCT and post-omalizumab treatment IgE values. This result reveals that patients with high IgE levels after omalizumab treatment have fewer urticarial symptoms than patients who remain at low IgE levels. Although there is currently no target level related to the IgE level intended to be reached, these data may conduct us in deciding to switch to alternative treatment options more rapidly, in a patient who can be mild to moderately controlled with omalizumab treatment.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data are openly available in a public repository that issues datasets with DOIs.

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Case Report

An Adverse Impact of Concurrent Cranial Irradiation Therapy and Phenytoin-Erythema Multiforme, Phenytoin, and Cranial Irradiation Therapy Syndrome

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Abstract

Prophylactic antiepileptics, especially phenytoin, are very commonly prescribed post brain tumor excision. Its concomitant use with radiotherapy (RT) increases its adverse effect profile and leads to skin lesions ranging from erythema multiforme, maculopapular eruption to SJS/TEN. Erythema multiforme, phenytoin and cranial irradiation therapy (EMPACT) syndrome is the term that describes this reaction. Herein, we report a case of EMPACT syndrome in a 32-year-old woman, receiving targeted RT and prophylactic antiepileptics post astrocytoma excision. The patient developed facial swelling more over the right side and blanchable erythematous maculopapular rash with atypical target lesions all over the body. These lesions were seen 1½ months post prophylactic phenytoin treatment and 7 days after targeted RT of the right frontal area. Immediate cessation of phenytoin, alternative antiepileptics, and systemic corticosteroids aided in complete recovery. EMPACT syndrome is a rare, but serious complication and clinicians should be made aware of this entity.

Keywords: Cranial irradiation therapy, cutaneous hypersensitivity, erythema multiforme

Introduction

Erythema multiforme, phenytoin, and cranial irradiation therapy syndrome (EMPACT syndrome) was first proposed by Ahmed *et al*. in 2004.[1] Higher risk of severe adverse drug reactions was reported in patients receiving cranial irradiation therapy and phenytoin, which suggested that anticonvulsants coupled with radiotherapy (RT) increase the adverse reaction potential of the anticonvulsant.[2,3] Here, we describe an interesting case of a patient with astrocytoma post excision, who developed erythema multiforme lesions while on prophylactic antiepileptics drugs (AED) and targeted RT. Over the past two decades, more than 30 such cases have been described.

Case Report

A 32-year-old woman presented with a history of fever, swelling of the face and eyelids, and itchy raised red rashes all over the body since 1 day. She had undergone surgical excision of right frontal diffuse astrocytoma (Grade 2) 1½ months back and postsurgery was started on prophylactic phenytoin 300 mg once a day and levetiracetam 750 mg twice a day for 1½ months. She was also treated with targeted RT over the right frontal area of the scalp 7 weeks after the surgery for 5 consecutive days. She developed the aforementioned symptoms 1 day after stopping RT.

On examination, she was found to be febrile and tachycardic. Erythema and edema of the face and eyelids were noted which were more pronounced over the right side [Figures 1 and 2]. Few pinpoint petechiae were noted over the hard palate [Figure 3]. Erythematous maculopapular blanchable rashes were present over the

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neck and trunk, and atypical target lesions were seen over her bilateral upper and lower limbs including palms and soles [Figures 4–6]. Conjunctival and genital mucosa were not involved. Nikolsky sign was negative. There was no lymphadenopathy. Rest of the systemic findings were within normal limits. Following the findings, a provisional diagnosis of drug reaction (drug reaction with eosinophilia and systemic symptoms) and erythema multiforme was made.

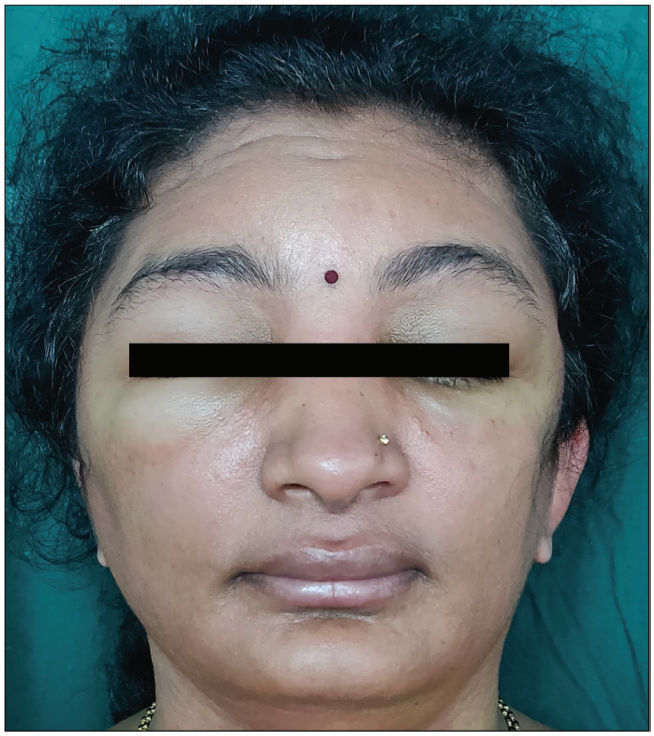

Figure 1: Edema and erythema noted over face which is more pronounced over the right side

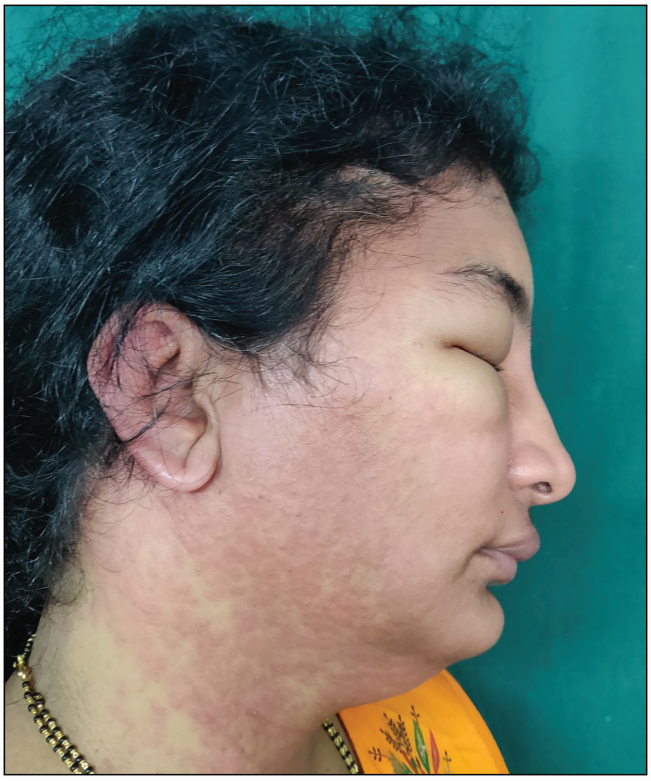

Figure 2: Erythema and edema noted over right ear

Routine blood tests showed a 10% increase in eosinophil count. Liver function tests were minimally deranged. Peripheral smear revealed relative neutrophilia. RegiSCAR criteria for DRESS were not met hence ruled out. Skin biopsy from the forearm revealed epidermal spongiosis, apoptosis of keratinocytes, few necrotic keratinocytes in the basal layer, tagging of lymphocytes along the dermoepidermal junction, edema of the superficial dermis with perivascular lymphocytic infiltrate, and extravasated erythrocytes suggestive of erythema multiforme. [Figure 7].

A neurology reference was sought for change of AEDs, following which safer alternative anticonvulsants were started. On admission, a high dose of corticosteroids was initiated but because of the persisting facial edema and periorbital puffiness, on physician's recommendation, a single dose of injection adrenaline 0.5cc intramuscularly was administered. Over the ensuing 7 days, systemic corticosteroids were tapered, resolution of the lesions occurred, and the patient was discharged from the hospital. A clinicopathological diagnosis of erythema multiforme was made, and a history of concurrent phenytoin treatment with RT aided in the ultimate diagnosis of EMPACT syndrome.

Discussion

Erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis are acute, life-threatening mucocutaneous syndromes frequently triggered by medications. Aromatic oral anticonvulsants (e.g., phenobarbital, phenytoin, and carbamazepine) are the drugs most frequently associated with these disorders.[4]

The important points to be considered in the diagnosis of EMPACT syndrome are as follows: lesions first start on radiation-exposed areas and then spread to the rest of the body, duration between the initial RT-AEDS and onset of skin rash is between 1 and 2 months. Finally, the lesions rapidly improved following the discontinuation of phenytoin.[5,6] In our case, the skin lesions developed over the radiation-exposed head area and gradually spread over the rest of the body, 1½ months following phenytoin treatment and 7 days post initiating RT. Tablet phenytoin and levetiracetam were immediately withheld and the patient was started on tablet lacosamide 100mg twice a day and clobazam 10mg once a day, following which the patient recovered well.

Ahmed *et al.* studied a case series of EMPACT syndrome wherein 16 (73%) of 22 individuals developed Stevens–Johnson syndrome, while the rest had erythema

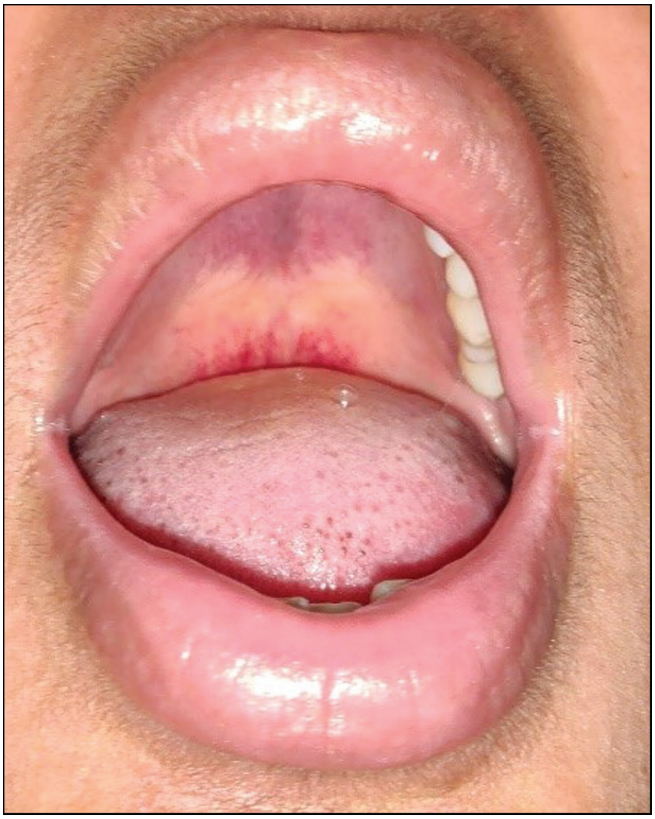

Figure 3: Few pin point petechiae noted over the hard palate

multiforme.[1] Delattre *et al*. described eight patients who developed erythema multiforme or Stevens–Johnson syndrome after receiving combination whole-brain radiation therapy and phenytoin.[7] Kazanci *et al*. reported a patient who developed erythema multiforme after administration of cranial irradiation and phenytoin treatment post temporal glial tumor excision.[8]

Radiation disrupts the metabolism of phenytoin and anticonvulsant medications. Normally, phenytoin and other anticonvulsants stimulate microsomal cytochrome 450(CYP)3A, resulting in oxidative intermediates that are then detoxified by epoxide hydrolase. A deficiency of this enzyme leads to increased intermediate metabolites, inhibits T-suppressor lymphocytes, and eventually activates an immune response leading to skin manifestations.[9,10] We present this report to emphasize the importance of close monitoring in patients receiving irradiation and drugs that induce cytochrome P 450.

EMPACT syndrome is an uncommon and potentially fatal form of cutaneous hypersensitivity. Clinicians should exercise caution while treating patients receiving phenytoin and radiation, and complications that arise should be managed aggressively. To lower the patient's morbidity profile, early detection, withdrawal of the offending medicine, safer AEDs, and active care are essential.

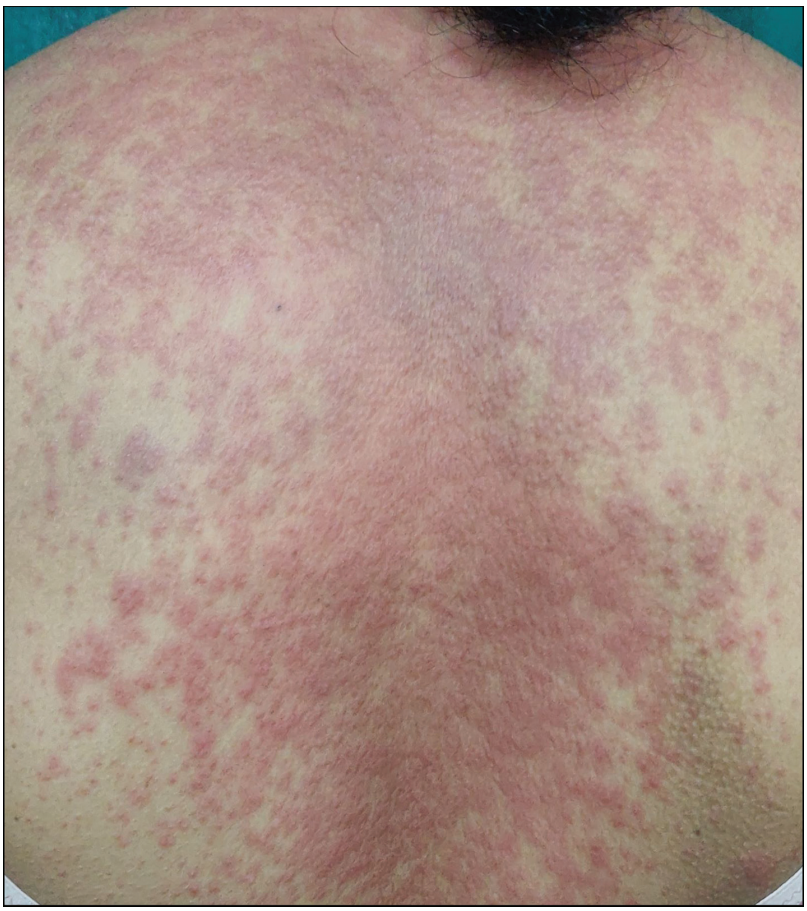

Figure 4: Erythematous maculopapular blanchable rashes with atypical target lesions noted over upper back

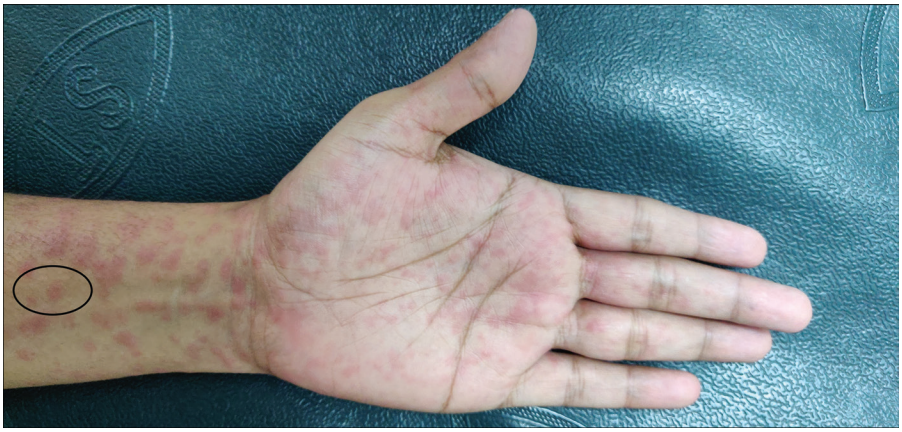

Figure 5: Erythematous maculopapular rashes with atypical target lesions over palms and forearms (see marked target lesions)

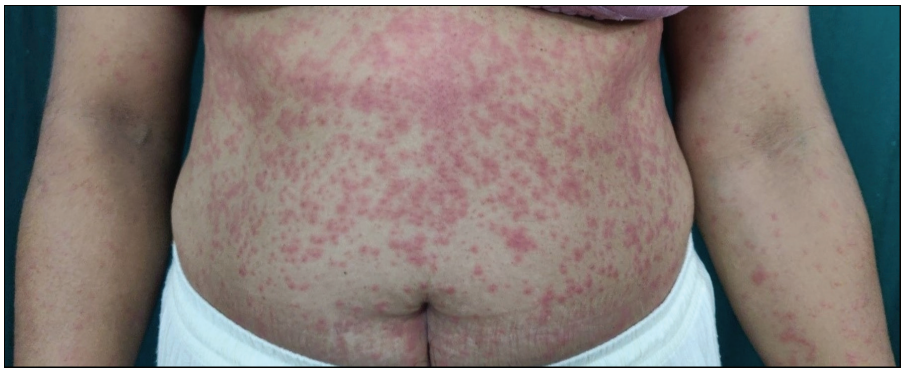

Figure 6: Erythematous rashes with few atypical target lesions over abdomen

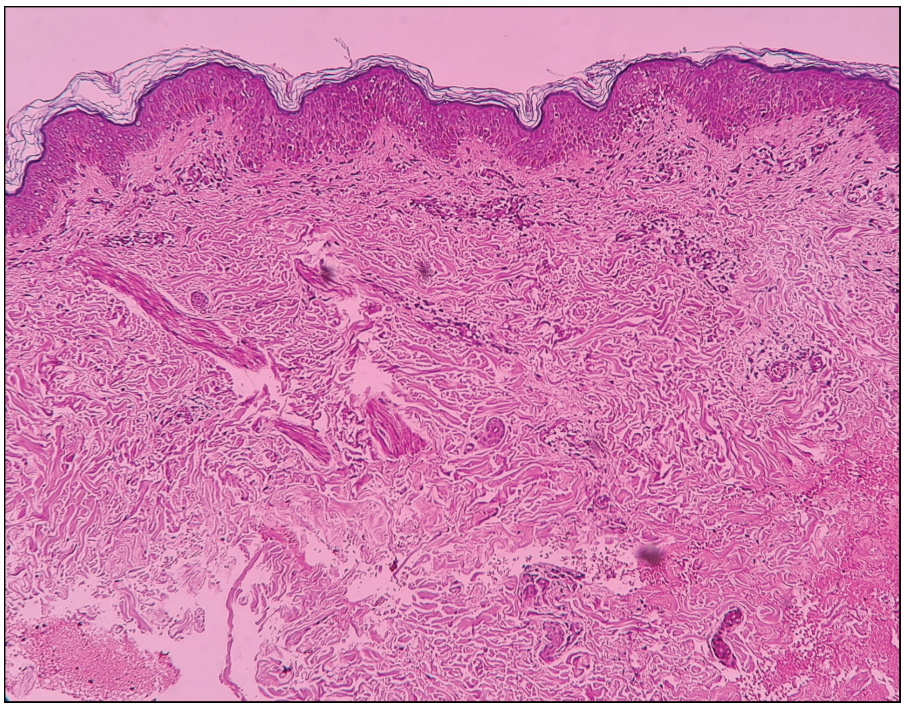

Figure 7: Epidermal spongiosis, edema of superficial dermis with perivascular lymphocytic infiltrate (H and E, ×10)

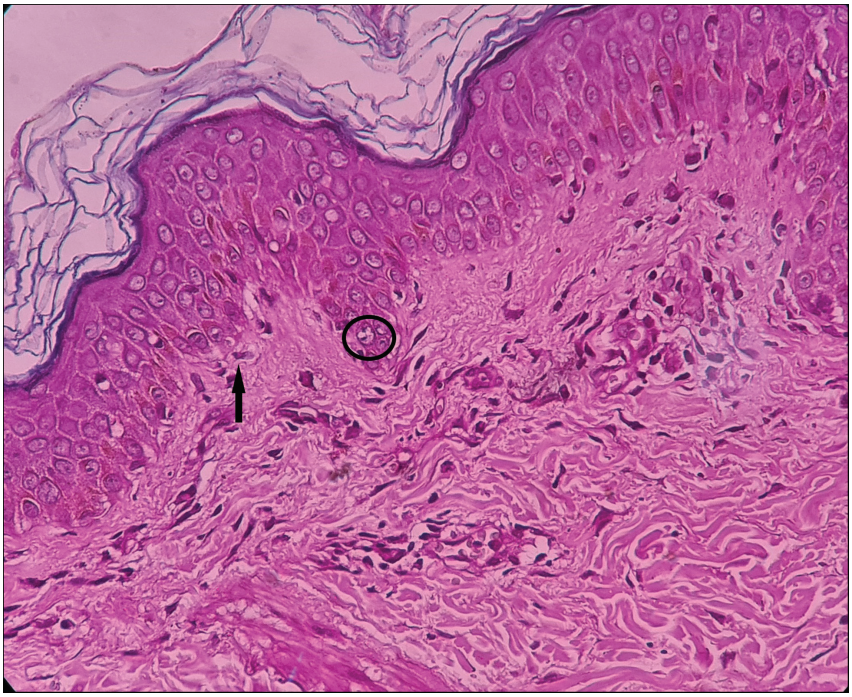

Figure 8: Few necrotic keratinocytes in basal layer (marked in black circle), tagging of lymphocytes along the dermoepidermal junction (black arrow) (H and E, ×40)

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Multiple Papulonodules over Face and Trunk: A Rare Case Report

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Abstract

Familial cylindromatosis (turban tumor syndrome) is a very rare neoplasm originating from eccrine or apocrine glands. It is an autosomal dominant condition, characterized by multiple cylindromas commonly presenting over face or scalp. We report a case of familial cylindromatosis diagnosed on the basis of clinical, dermoscopic, and histopathological findings in a 70-year-old female. The case is reported due to its rare occurrence in Indian scenario.

Keywords: Dermoscopy, familial cylindromatosis, jigsaw puzzle, turban tumor

Introduction

Cylindromas are benign skin appendageal neoplasms most likely originating from eccrine glands.[1,2] They can be single or multiple, commonly involving scalp, face, and neck. Solitary cylindromas occur sporadically, whereas multiple tumors are inherited in an autosomal dominant manner. Multiple lesions over scalp present as numerous small papules and/or large nodules over the scalp like a turban, hence commonly known as turban tumor. Familial cylindromatosis (FC), originally described as Ancell–Spiegler cylindroma, is a rare autosomal condition with apparently complete penetrance but variable expression characterized by multiple cylindromas over face and scalp.[3]

Case Report

A 70-year-old female born out of non-consanguineous marriage presented to us with multiple asymptomatic skin-colored to reddish raised lesions over scalp, face, and trunk since 40 years. These lesions first appeared when she was 30 years old, primarily on face and scalp, which gradually increased in size and number over the years to involve trunk. There was history of intermittent bleeding from larger lesions since 2–3 years. Similar history of lesions was also present in her grandmother, elder sisters, and daughter [Figure 1]. On cutaneous examination, there were multiple confluent skin-colored to erythematous, smooth surfaced, rounded, firm, non-tender papulonodules of varying sizes ranging from 0.5 to 5 cm in diameter with overlying telangiectasias in few lesions present predominantly over face, left half of scalp, right retroauricular, infraauricular, preauricular region, neck, chest, upper, and lower back, bilateral groin folds, and vulva [Figure 2a-g]. There was a single pedunculated nodule of size 3 × 2 cm over left side of the chin. Single well-defined, hyperpigmented, non-umbilicated nodule is present near right nasal fold. Rest of the cutaneous examination was unremarkable. General and systemic examination was normal. Based on history and clinical presentation, differential diagnoses of cylindromas, trichoepitheliomas, and spiradenomas were considered [Table 1]. Dermoscopy was performed using 3Gen DermLite DL4 (CA, USA) in 10× polarized mode. Dermoscopy of most of the nodular lesions over back revealed arborizing vessels on whitish pink background with blue dots and globules. Dermoscopy of few lesions over face and upper trunk revealed arborizing vessels on whitish pink background with ulceration and yellow

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non-homogeneous areas at places [Figure 3a-d]. Fine needle aspiration cytology (FNAC) from nodules over scalp, right nasolabial fold, and back revealed basaloid cells in clusters, acinar pattern around small hyaline globules, and lining ribbons of hyaline material. Few clusters and dispersed cells with scanty cytoplasm and oval hyperchromatic nuclei with granular chromatin seen are suggestive of cylindroma [Figure 4a and b]. Local USG of the lesions revealed multiple, round to oval, hypoechoic lesions in subcutaneous plane and normal parotid regions [Figure 5a and b]. Computed tomography of head, neck, and thorax was normal. Histopathological examination from nodule over back and face revealed epidermis showing basket weave hyperkeratosis, poorly circumscribed tumor comprising irregularly shaped islands, and cords of basaloid cells with peripheral palisading by eosinophilic hyaline bands in dermis suggestive of cylindroma [Figure 6a-c]. Routine hematological investigations were within normal limits. On the basis of clinical, dermoscopic, cytological, and histopathological findings, a final diagnosis of familial cylindromatosis was reached. Gene mapping was not done due to limited resources. The patient was referred to plastic surgery for further management.

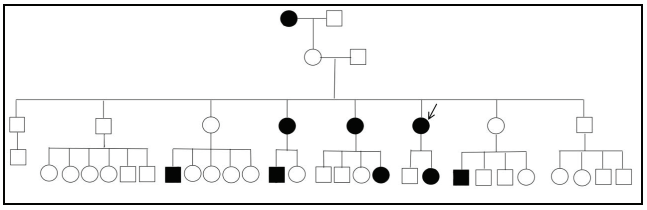

Figure 1: Pedigree chart showing similar lesions in grandmother, elder sisters, and daughter

Discussion

Ancell[4] first described cylindroma in 1842. Cylindromas are benign skin appendageal tumors originating most

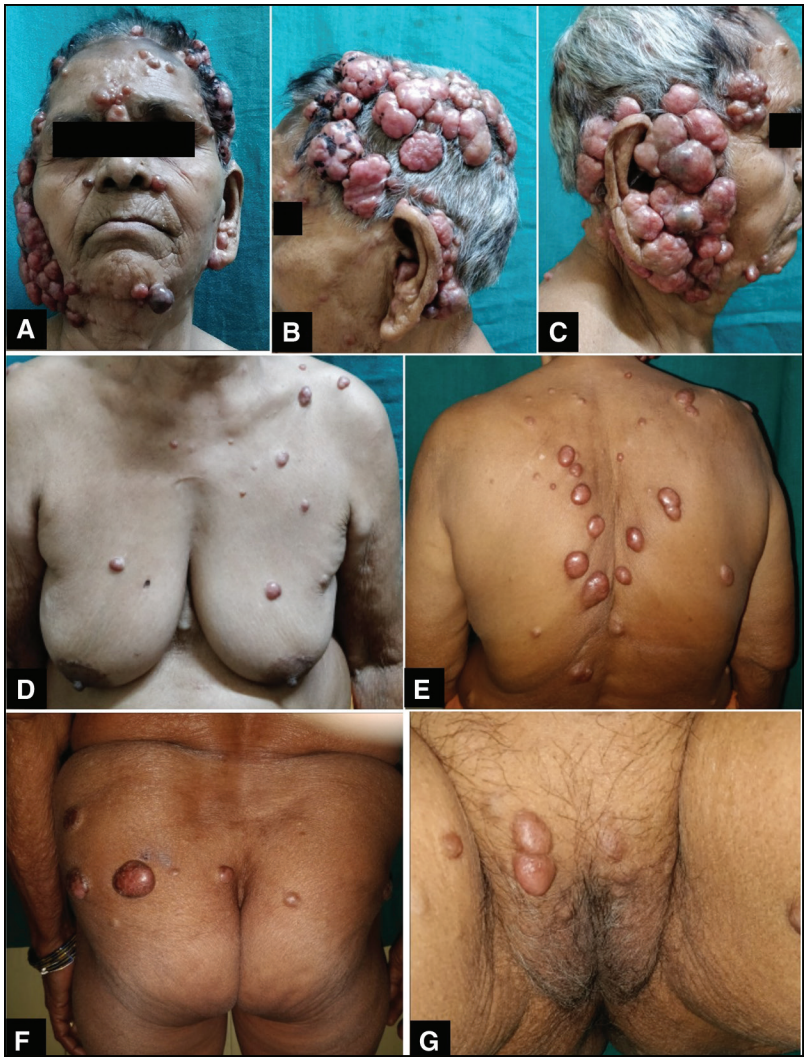

Figure 2: (a-g) Multiple confluent skin colored to erythematous, smooth surfaced, rounded, firm, non-tender papulonodules of varying sizes with overlying telangiectasias in few lesions over face (a), left half of scalp (b), right auricular region (c), neck, chest (d), upper (e) and lower back (f), bilateral groin folds and vulva (g)

Table 1: Differential diagnosis of cylindroma

	Spiradenoma	Cylindroma	Trichoepithelioma
Clinical appearance	Soft, blue, gray, or purple nodule, painful on palpation, located on head, neck or trunk.	Firm, pink, red, or blue nodule located on the face or scalp	Round, skin-colored, firm papules or nodules located on the nasolabial folds, nose, forehead, upper lip, and scalp.
Histology	Two types of tumor cells: basaloid cells contain a small, hyperchromatic nucleus with scant cytoplasm. Other cells are larger and contain a pale nucleus. Thin basal membrane. Frequent lymphocytic infiltration	Small lobules of basaloid cells arranged in a jigsaw pattern and surrounded by a prominent hyaline basement membrane. Absence of inflammatory infiltrate	Nests of basaloid cells with horn cysts in dermis. Tumor cells have minimal cytoplasm and a large hyperchromatic nuclei and show peripheral palisading. Formation of dense aggregates of fibroblastic cells referred to as papillary mesenchymal body.
Dermoscopic features	Light blue pigment with peripheral reticulate pigmentation, associated with reddish linear serpentine structures surrounded by whitish areas	Blue dots and globules associated with arboriform vessels on a whitish, salmon-pink background	Arborizing vessels, multiple milia-like cysts, and rosettes amidst a whitish background

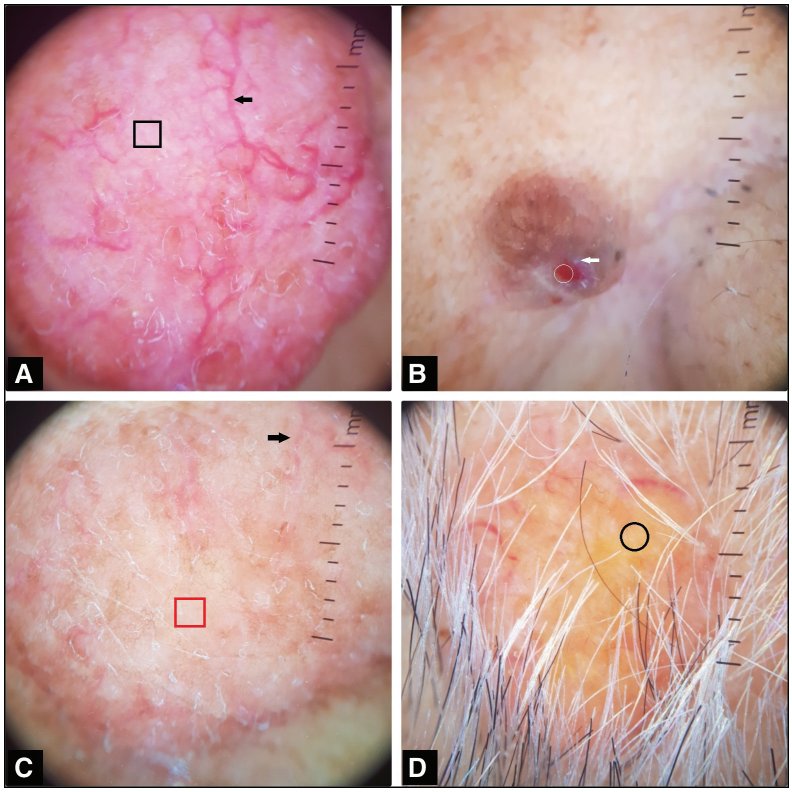

Figure 3: (a-d) Dermoscopy [3Gen DermLite DL4 (CA, USA) 10× polarized mode] of lesions over face and upper trunk revealed arborizing vessels (black arrow) on whitish pink background (black box) with blue dots and globules (white arrow). Dermoscopy of lesions over back revealed arborizing vessels on whitish background (red box) with ulceration (white circle) and yellow non-homogeneous areas at places (black circle)

commonly from folliculo-sebaceous-apocrine unit. It is usually seen in middle aged females with scalp being the most common site. Cylindroma has two types of clinical presentations: a solitary form, without family history of cutaneous cylindromas, most commonly involving skin of the head and neck.[1] Solitary (sporadic) form occurs as frequently as the multiple form. Multiple, inherited cylindromas are more common in females and occur over a wide age range, with the majority of patients in second or third decades of life, as seen in our case, which increase in size and number throughout life.[1,2] These may occur on the scalp and rarely on the trunk and the extremities.[1] Cylindroma presents as slow growing, multiple, pink to red, firm, smooth surfaced papules and nodules, often pedunculated with surface telangiectasias. Although rare, malignant transformation can be seen in multiple cylindromatosis.[5,6] Thus patients are at risk of developing tumors such as basal cell adenoma and adenocarcinoma of parotid and minor salivary glands. Multiple cylindromas can occur as a part of FC, Brooke–Spiegler syndrome (BSS) and multiple familial trichoepitheliomas.[7] All the three have been recently associated with mutations in the CYLD gene.[3] The tumor suppressor gene, cylindromatosis gene (CYLD1), is located on band 16q12-13.[8] The gene

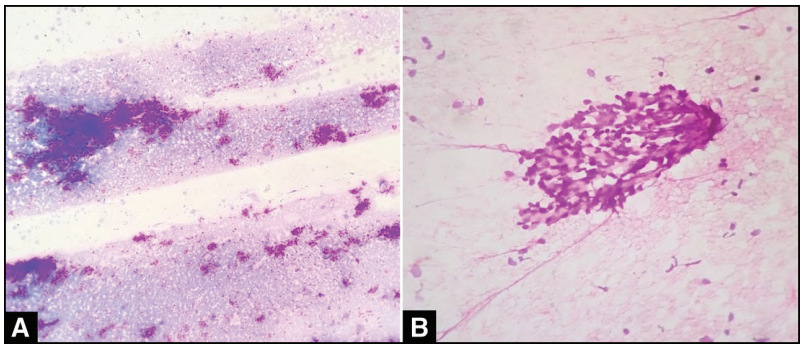

Figure 4: (a, b) FNAC from nodules over scalp, right nasolabial fold and back revealed basaloid cells in clusters, acinar pattern around small hyaline globules, and lining ribbons of hyaline material. Few clusters and dispersed cells with scanty cytoplasm, oval hyperchromatic nuclei with granular chromatin seen suggestive of cylindroma

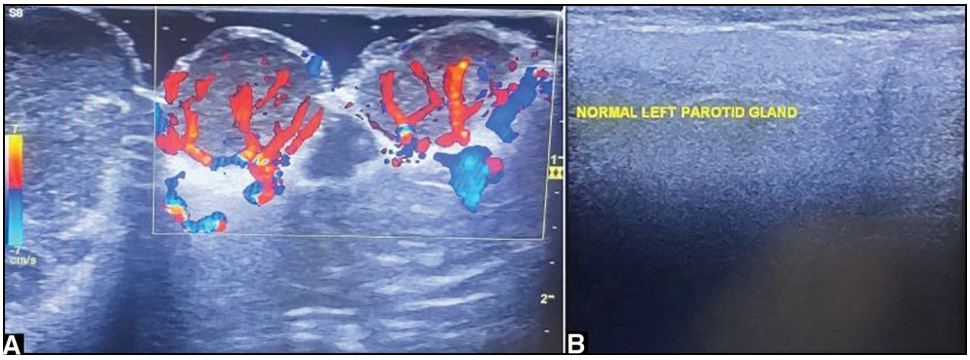

Figure 5: (a, b) Local USG of the lesions revealed multiple, round to oval, hypoechoic lesions in subcutaneous plane (a) and normal parotid regions (b)

product represses the TNFα pathway which regulates a number of antiapoptotic genes involved in proliferation of skin appendages by increasing the expression of nuclear factor κ-β.[7,8] BSS is an inherited disease characterized by multiple skin appendageal tumors predominantly cylindromas, trichoepitheliomas, and/or spiradenomas.[3,8] Histopathology of cylindroma reveals sharply circumscribed nodules within the dermis and/or subcutis composed of nests of basaloid cells arranged in a jigsaw puzzle pattern, as seen in our case. The cells are of two types: one large, with a moderate amount of cytoplasm and a vesicular nucleus arranged centrally; and the other small, with little cytoplasm and a compact nucleus arranged peripherally. Jarrett *et al.* were the first to describe dermoscopy of cylindroma.[9] On dermoscopy, the reported patterns of cylindroma consist of arborizing vessels on whitish pink background, blue dots and globules, ulceration, and yellowish non-homogeneous areas correlating to hyperkeratosis as observed in our case.[9-11] Similar dermoscopic patterns have also been reported in basal cell carcinoma.[12] The vascular patterns and color of dots and globules may help to differentiate cylindromas and nodular basal cell carcinoma. The vascular branches are more pronounced at the periphery and they extend from the periphery toward the center of the lesion in cylindromas while arborizing vessels are more pronounced towards center without any particular pattern in basal cell carcinoma.[10] Also, blue dots/globules are visible in cylindroma in contrary to gray dots in basal cell carcinoma.[11] Treatment of choice for cylindroma is surgical excision or laser ablation. Alternative treatment includes cryotherapy, electrosurgery, carbon dioxide laser, radiotherapy, and dermabrasion.[7] To prevent occurrence of new lesions, topical aspirin derivatives are currently being tried.[6] Regular follow-up is required in such cases to rule out malignant transformation. Dermoscopy can aid in the diagnosis of cylindroma in rare cases. There are very few reports of clinico-dermoscopic patterns describing multiple familial cylindromatosis in India [Table 2]. Thus we report a case of familial cylindromatosis affecting trunk along with scalp and face with strong family history and without associated other adnexal neoplasm.

Acknowledgments

We express our thanks for providing histopathology and cytology images to Department of Pathology and for providing radiological images to Department of Radiology of Government Medical College, Nagpur.

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Nil.

Conflicts of interest

There are no conflicts of interest.

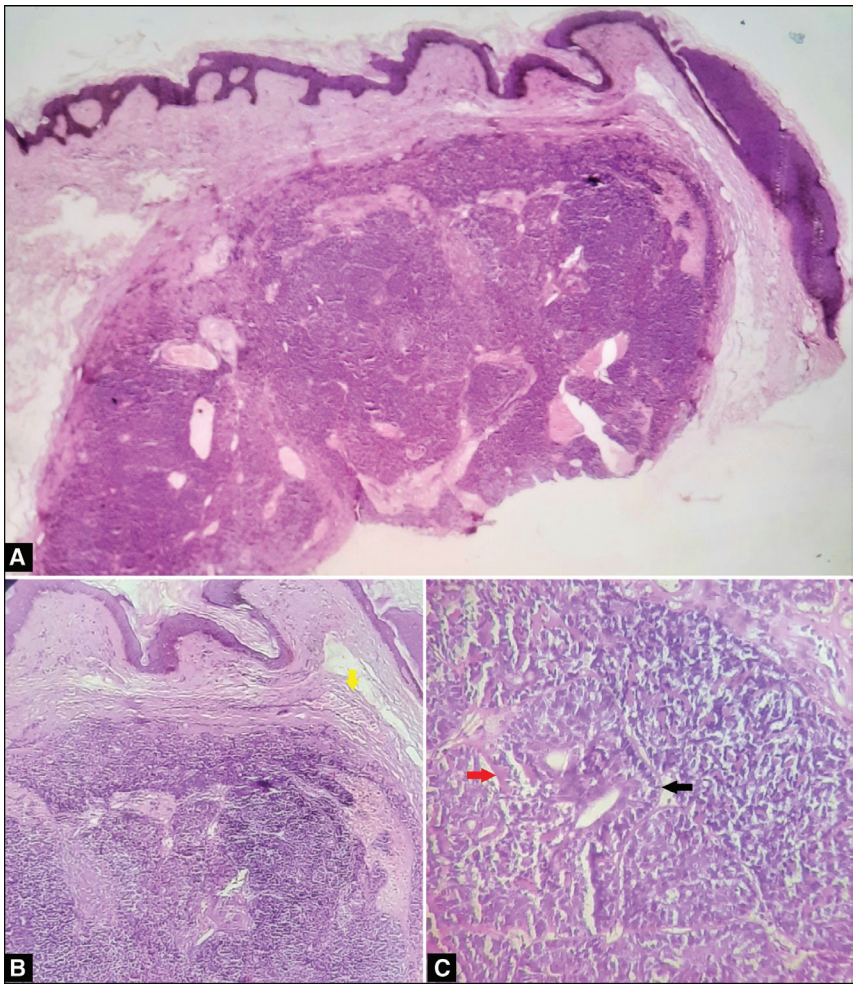

Figure 6: (a-c): Histopathological examination from nodule over back and face revealed epidermis showing basket weave hyperkeratosis (yellow arrow), poorly circumscribed tumor comprised irregularly shaped islands and cords of basaloid cells with peripheral palisading (black arrow) by eosinophilic hyaline bands (red arrow) in dermis suggestive of cylindroma

Table 2: Literature review of dermoscopic patterns of cylindromas

Sr no.	Case report	Year	Age/sex	Description	Findings on dermoscopy
1	Jarret *et al.*	2009	42/F, 45/F	Dermoscopy of BSS[9]	Areas of pink background with ill-defined arborizing vessels and ill-defined blue structures
2	Cabo *et al.*	2010	80/F	Dermoscopy of cylindroma[13]	Areas of pink background coloration, arborizing telangiectasia, blue dots/globules, and ulceration
3	Lallas *et al.*	2011	58/F	Dermoscopy of solitary cylindroma[10]	Arborizing telangiectatic vessels, with a relatively small number of branches, on a homogeneous white-pinkish background. The vessels appeared blurred and light-red-to-pinkish in color and were observed mainly at the periphery of the lesion
4	Cohen *et al.*	2014	65/M	Dermatoscopic pattern of a cylindroma[11]	Arborizing telangiectasia and several scattered white globules on a white to salmon pink background
5	Tiodorovic *et al.*	2015	43/F, 37/F	Clinical, histological, and dermoscopic findings in familial cylindromatosis: a report of two cases[14]	Arborizing vessels on a white-ivory or pinkish background, more prominent at the periphery of lesions, in some tumors blue dots and globules were also present

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An Extremely Uncommon Case of Giant Cell Tumor of Skin: A Case Report in a 16-year-old Female

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Abstract

Giant cell tumors of the skin are known to be extremely rare tumors, grossly, and histologically similar to that of giant cell tumors of bone. A 16-year-old girl presented with an asymptomatic swelling over the right cheek, which had progressed over 5 months duration without any antecedent history of local trauma and infection. Grossly, the specimen was brown-colored without any pigmentation, fleshy, and consisted of a skin-covered globular mass measuring 1.5 × 1.0 × 0.5 cm. On histopathologic examination, sections examined show a well-circumscribed lesion involving the dermis and revealed biphasic population of round to spindle-shaped mononuclear cells with intimately admixed osteoclast-like giant cells. On immunohistochemistry, osteoclast-like giant cells and mononuclear cells showed strong cytoplasmic granular positivity for CD68 and final diagnosis of giant cell tumor was given.

Keywords: CD68, giant cell tumor, osteoclast-like giant cells

Introduction

Giant cell tumors of the skin are known to be extremely rare tumors, involving commonly the extremities, head, and neck regions, which are grossly and histologically similar to that of giant cell tumors of bone.[1] Histologically, these tumors show round- to spindle-shaped cells admixed with uniformly scattered osteoclast-like multinucleated giant cells.[2] To the best of our knowledge, less than 10 cases of this entity have been reported in the literature so far. We report the clinical and histologic features of giant cell tumor of the skin in a 16-year-old girl, which is believed to be the ninth reported case of giant cell tumor of skin as a primary lesion at this site [Table 1].

Case Report

A 16-year-old girl presented with an asymptomatic swelling over the right cheek on the facial region, which had progressed over 5 months duration without any antecedent history of local trauma and infection. On local examination, the swelling was well-circumscribed, no skin color changes (similar to adjacent skin), no ulceration, mobile, nontender, adherent to skin, and measuring about 2.0 × 1.5 × 1.0 cm in size. No regional lymph nodes were involved. X-ray showed no bony involvement. The clinical diagnosis of granulomatous lesion of skin was given. The lesion was excised and sent for histopathologic examination. Grossly, the specimen was brown-colored without any pigmentation, fleshy, and consisted of a skin-covered globular mass measuring 1.5 × 1.0 × 0.5 cm. On histopathologic examination, sections examined show a well-circumscribed lesion involving the dermis and revealed biphasic population of round- to spindle-shaped mononuclear cells with intimately admixed osteoclast-like giant cells [Figures 1–3]. The cells had a moderate amount of granular eosinophilic cytoplasm and oval- to spindle-shaped nuclei with vesicular chromatin and prominent nucleoli. The tumor giant cells had multiple nuclei similar to those of mononuclear cells and eosinophilic granular cytoplasm. The mononuclear cells showed mild pleomorphism and occasional mitotic activity.

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A provisional diagnosis of giant cell tumor of the skin was made. On immunohistochemistry, osteoclast-like giant cells and mononuclear cells showed strong cytoplasmic granular positivity for CD68 [Figure 4] and final diagnosis of giant cell tumor was given.

Discussion

Giant cell tumors of the skin, which are extremely rare tumors, resembles their osseous variants both grossly and histologically. Age of presentation of these tumors is 68–78 years (median age 73 years) with an M:F ratio of 3:2.[1,6] In 1972, Salm and Sissons[7] first described the giant cell tumor of soft tissue, which formerly comes under the term "malignant giant cell tumor of soft parts." Guccion and Enzinger reported the tumor of soft tissue with the same characteristic features but with aggressive malignant transformation as atypia, abundant mitotic activity, and pleomorphism.[8] Folpe *et al.* reclassified them as "giant cell tumor of low malignant potential" because on further pathological analysis they found lack of cytological atypia even with increased mitotic activity and vascular invasion.[9] The extremities, head, and neck are commonly involved sites by this tumor. These tumors are well-circumscribed, unencapsulated, and multinodular with a mixture of round- to spindle-shaped mononuclear neoplastic cells and osteoclast-like giant cells scattered uniformly. Osteoclast-like giant cells have voluminous eosinophilic cytoplasm with 50–100 small nuclei, which arise due to fusion or by amitotic nuclear division of precursor mononuclear cells. The histogenesis is not clear. However, previously it was considered as one of the histologic types of malignant fibrous histiocytoma but not favored so long.[3] The osteoclast-like giant cells and mononuclear cells show strong positivity for CD68, alpha-1 antitrypsin, and alpha-1 antichymotrypsin, whereas these cells are negative for cytokeratin (AE1/AE3) and S100 protein.[2] Differential diagnosis of this tumor includes benign fibrous histiocytoma, atypical fibroxanthoma, and giant cell tumor of bone with soft tissue extension. Benign fibrous histiocytoma with many osteoclast-like giant cells can be differentiated by the presence of hyperplastic epidermis, hyperpigmentation of

Table 1: Brief review of giant cell tumors of skin

Study	Patient age in years	Sex
Hoang *et al*. (2002)[2]	6–78 (Five cases)	3 Male and 2 Female
Kumar *et al*. (2006)[3]	55	Male
Lentini *et al*. (2010)[4]	79	Female
Murphy *et al*. (2011)[5]	92	Female
Present case	16	Female

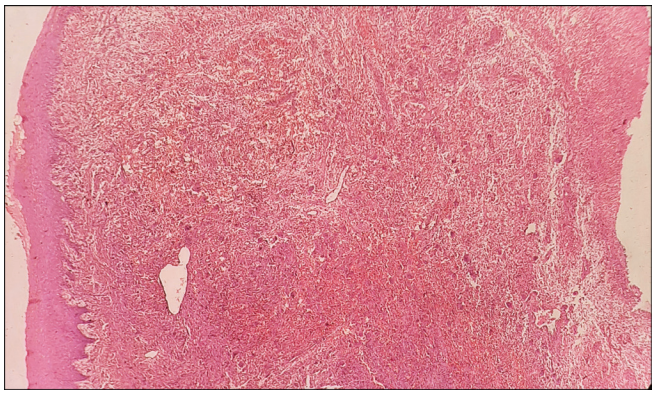

Figure 1: Well-circumscribed lesion involving dermis (H&E, 4X).

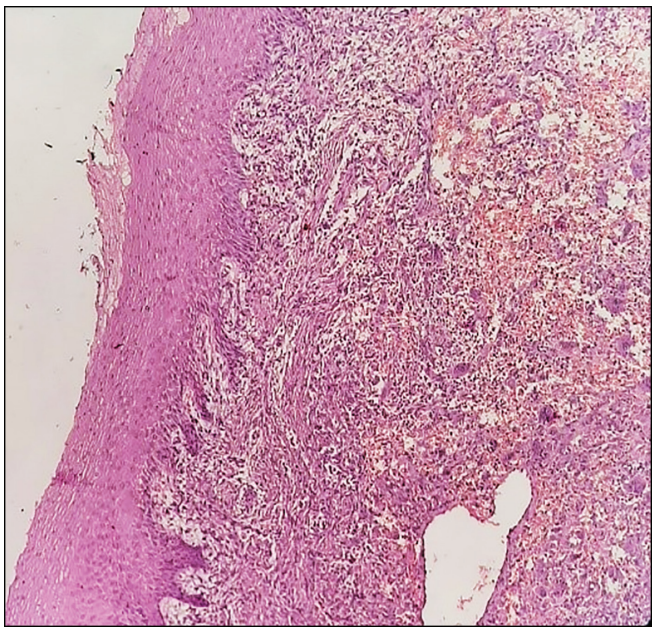

Figure 2: Epidermis along with mononuclear cells and admixed osteoclast-like giant cells with hemorrhage in dermis (H&E, 10X).

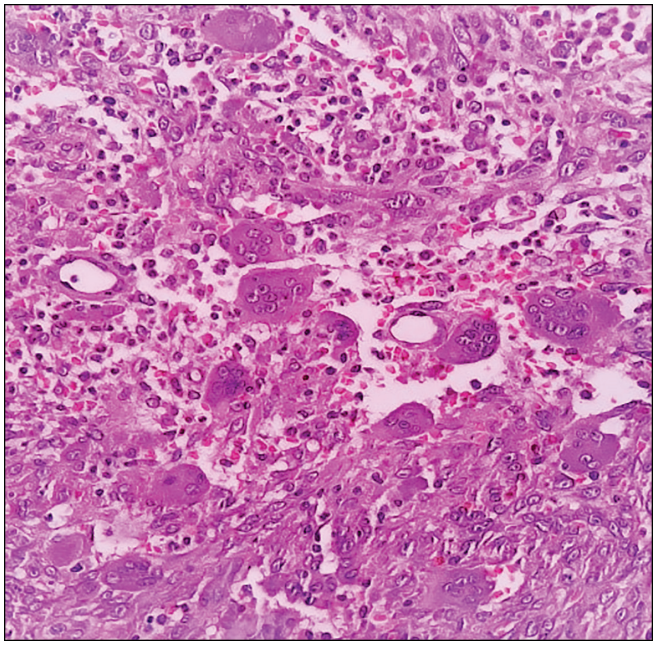

Figure 3: Biphasic population of round to spindle-shaped mononuclear cells with intimately admixed osteoclast-like giant cells (H&E, 40X).

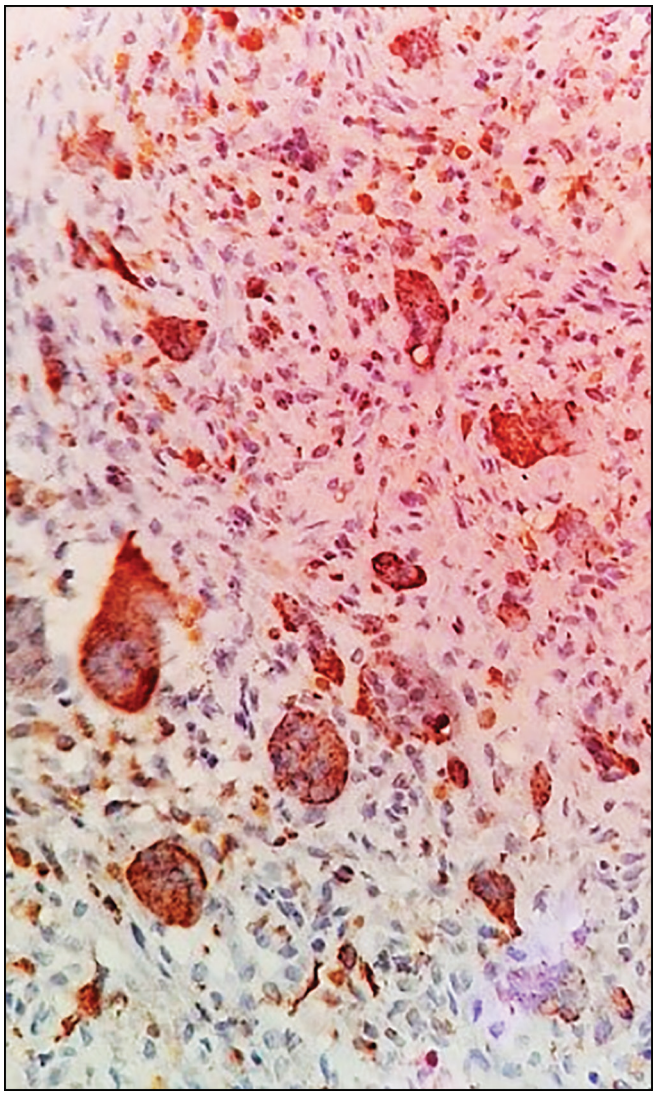

Figure 4: Osteoclast-like giant cells and mononuclear cells showing cytoplasmic granular positivity for CD68 (IHC, 40X).

the basal layer, and elongation of rete ridges.[10] Atypical fibroxanthoma shows pleomorphic histiocytes-like cells and atypical giant cells, often with bizarre nuclei and numerous mitotic figures.[2,10] Giant cell tumor of bone with soft tissue extension shows radiologically, an osteolytic lesion in epiphysis and presence of a rim of ossification at the edge of the tumor.[11] Extraskeletal osteosarcoma can be differentiated by the presence of neoplastic bone or osteoid.[12] Both benign fibrous histiocytoma and atypical fibroxanthoma show resemblance with this tumor and can only be differentiated by histopathologic studies. Giant cell tumor of bone also shows a lot of similarities with tumor and radiologic studies are needed to differentiate between both of them. Cutaneous giant cell tumors are low-grade sarcomas that can recur locally and infrequently metastasize. One case with lung metastasis has been reported in the literature. Superficial tumors have a better prognosis than deeper ones; 75% of superficial tumors recur and 25% metastasize, whereas about 50% of deep tumors recur and about 50% metastasize.[2]

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Conflicts of interest

There are no conflicts of interest.

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