DOD Clinical Case Report
2017; 1: 24-31 ***doi:***

Case Report

AN UNUSUAL MANIFESTATION OF LATENT TUBERCULOSIS INFECTION: ERYTHEMA INDURATUM OF BAZIN

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ABSTRACT
Erythema induratum of Bazin is characterized by tender, erythematous to violaceous subcutaneous nodules that usually occur on the lower legs. Currently the terms EIB and nodular vasculitis are often used as synonyms to describe this most common type of lobular panniculitis. However, some investigators still prefer the name EIB for those cases associated with tuberculosis infection. We describe 5 consecutive cases of EIB presented in the last seven months beginning from winter 2009 to autumn 2010. All patients had tender, erythematous to violaceous nodules on the lower legs. One patient had a history of a long- term cough one year ago, whereas 4 had a positive family history for tuberculosis. Tissue polymerase chain reaction were studied for 2 patients and revealed positive results while interferon-γ releasing assay resulted positive in all of the 4 patients tested. In addition, tuberculin skin test which was applied to 3 patients resulted with 15 mm, 20 mm, and 25 mm indurations. We found it suprising and worth mentioning that in the last 7 months, 5 consecutive patients who sought medical advice for tender, erythematous nodules on the lower legs appeared to have the diagnosis of EIB. Detailed personal and family history for tuberculosis infection was the most important clue that led to the diagnosis of EIB. In the light of these 5 cases, we would like to remind EIB which has to be kept in mind in the differential diagnosis of the patients with panniculitis like lesions especially in endemic areas for tuberculosis .

Key words: Erythema induratum of Bazin, tuberculosis, unusual manifestation

ÖZET
Eritema induratum Bazin (EİB) çoğunlukla alt bacaklarda hassas eritemli mor renkli subkutan nodüllerle karakterizedir. Günümüzde EİB ve nodüler vaskülit sıklıkla en çok görülen lobuler panniküliti tanımlamak için eşanlamlı olarak kullanılmaktadırlar. Ancak yine de bazı araştırıcılar tuberküloz enfeksiyonu ile birliktelik göstereren olguların EİB olarak adlandırılmasını tercih etmektedirler. Biz son 7 ay içinde 2009 kışından başlayıp 2010 Ağustosuna kadar ortaya çıkan 5 ardışık olguyu açıkladık. Tüm hastalarda alt bacaklarda hassas eritemli mor renkli nodüller vardı. Bir hastanın bir yıl önce uzun süreli bir öksürük öyküsü varken diğer 4 hastada tüberküloz için pozitif aile öyküsü vardı. Doku polimeraz zincir reaksiyonu 2 hastada çalışılıp pozitif reaksiyon verirken interferon- γ releasing assay çalışılan 4 hastanın tümünde de pozitif sonuçlandı. Ek olarak, tüberkülin deri testi uygulanan 3 hastada, 15 mm,20 mm ve 25 mm endürasyonla sonuçlandı Biz son 7 ayda arka arkaya alt bacaklarda hassas eritemli nodüller için tıbbı tavsiye arayan ve EİB tanısı alan 5 ardışık hastayı şaşırtıcı ve üstünde durmaya değer bulduk. Ayrıntılı kişisel ve ailesel tüberküloz öyküsü EİB tanısına götüren en önemli ipucuydu. Bu 5 olgu ışığında özellikle tuberkükoz için endemik olan bölgelerde pannikülit benzeri lezyonlarda ayırıcı tanıda EİB'nin akılda tutulması gerektiğini hatırlatmak istedik.

Anahtar kelimeler: Erythema induratum of Bazin, tüberküloz, nadir klinik görünüm

INTRODUCTION

Erythema induratum of Bazin (EIB) was first described by Ernest Bazin in 1861 as "erythematous benign scrofulid appearing on legs in association with pulmonary tuberculosis".[1] Typical features of EIB are erythematous to violaceous subcutaneous nodules appearing on the lower legs of young to middle- aged women. The feet, thighs, arm and face are rarely affected. The lesions are characteristically recurrent, cold and sometimes tender. The superficial skin tends to show desquamation, crusting, or ulceration leaving postinflammatory hyperpigmentation and sometimes atrophic scars. [1]

The etiopathogenesis of EIB and its relation with tuberculosis is still controversial. In the early 20th century, Whitfield[3] and Galloway[4] pointed out that there were two variants of EIB, one related to tuberculosis and the other unrelated to tuberculosis. To differentiate the EIB from the non-tuberculosis variant, the term erythema induratum of Whitfield was proposed. Montgomery et al.[5] described the term nodular vasculitis for those patients in whom associated tuberculosis infection could not be demonstrated.[6] Type III and type IV hypersensitivity reactions to *Mycobacterium tuberculosis* are considered as the main immunologic mechanism involved in the pathogenesis EIB. [7,8] Recently, several studies detecting the mycobacterial DNA in skin lesions of EIB by polymerase chain reaction (PCR) have been reported.[9] Detection of mycobacterium DNA by PCR analysis in tissue examples has exacerbated the discussion about the relationship between tuberculosis and EIB. In general, EIB is acceppted to be a mostly lobular panniculitis which shows vasculitis, granulomatous inflammation, and necrosis.[2]

The aim of this study was to discuss the stepwise approach which is necessary to diagnose EIB; including history, physical examination, histopathology and appropriate laboratory and update the current therapeutical approach for EIB.

CASE REPORT

Demographic data and laboratory together with radiologic data that belong to 5 patients including the representative case are summarized in Table 1.

Representive Case (*Patient 1*)

A 46- year- old woman presented with recurrent, tender, erythematous nodules on the lower extremities and arms over a period of 5 years. Lesions resolved spontaneously approximately within 6 months. Although the lesions had neither ulceration nor discharge, most left atrophic scars. There was no history of night sweats, weight loss, fever or cough. Her past medical history was unremarkable while her family history revealed that her grandmother was operated for intestinal tuberculosis one year ago, her aunt and uncle died due to pulmonary tuberculosis and her brother was treated for tuberculosis 20 years ago.

Table 1. Demographic, laboratory and radiological findings of the patients

PatientNo	Age (year-old)/ Gender	Disease duration (months)	Personal history for tuberculosis	Family history for tuberculosis	Localization of erythematous tender nodules	TST/ mm	Thorax CT/Chest X ray	İnterferon-γ releasing assay	PCR analysis from skin biopsies
Case 1	46/F	60	Unremarkable	Grandmother, uncle, aunt, brother	Posterolateral aspects of the lower legs and arms	15	Nodules (<5mm) on both side of the lungs, calcified nodule on left side of the lung, and pleural plaques	NA	Negative
Case 2	31/F	60	Unremarkable	Grandfather, Sister of her mother	Anterior and posterior aspects of the lower legs and arms	NA	Normal x ray	Positive	Positive
Case 3	54/M	3	Unremarkable	Mother	Posterior aspects of the lower legs	20	Ipsilateral bullous changes	Positive	NA
Case 4	40/M	120	Unremarkable	Aunt	Anterior and posterior aspects of the lower legs.	NA	Normal x ray	Positive	NA
Case 5	46/M	18	History of a long period of cough one year ago	None	Posterolateral and posterior aspects of the lower legs	25	Calcified nodule on the left side of the lung and, atelectasis on the right lung side	Positive	NA

On dermatological examination, there were well-defined erythematous to violaceous nodules and atropic scars on the posterior aspect of the left leg, over the left knee and proximal aspect of the right arm. A punch biopsy of the lesion on the

posterior aspect of the left leg revealed lymphohistiocytic infiltration and giant cells around the vessels which extend from dermis to subcutaneous adipose tissue forming granulomas consistent with mostly lobular panniculitis. Initial investigations, including a complete blood count, erythrocyte sedimentation rate and C-reactive protein were within normal limits, as well as chest-X ray. Nodular lesions smaller than 5.5 mm on both side of the lungs, a calcified nodule on the left side and bilateral pleural plaques were identified on the examination of computed tomography (CT) of the thorax. Tuberculin skin test (TST) was positive with an induration of 20 mm. Based on these histopathological, laboratory, and clinical findings, the diagnosis of EIB was made. The patient was started on isoniazid 300mg/day and rifampicin 600mg/day for the following 3 months. The lesion resolved within the first month and did not appear in the following year except one lesion occurring in the 3rd month which resolved spontaneously.

Figure 1a and b represent the pictures of Case 3 before treatment and after a 3-month therapy and Figure 2 represents the histopathological examination of the same patient. All of the four patients except patient 1 were started on antituberculosis medication with 4- drug regimen (isoniazid 300mg/day, rifampicin 600mg/day, ethambutol 2000 mg/day and pyrazinamide 1500mg/day) for 2 months followed by dual therapy with rifampicin and isoniazid for the subsequent 4 months. All of these four patients had complete resolution of their symptoms after treatment.

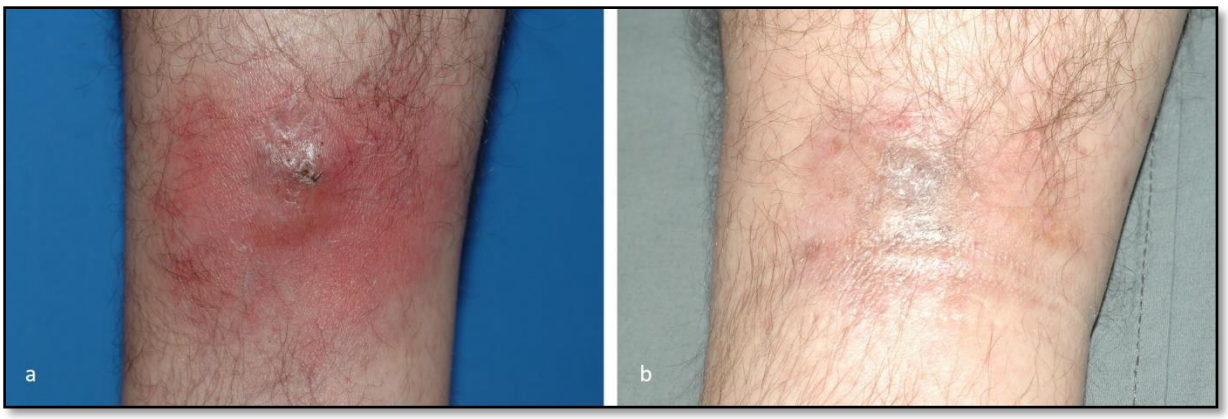

Figure 1. a) Well-defined erythematous nodule on the posterior aspect of the lower leg of Case 3, b) An hyperpigmented atrophic scar on the posterior aspects of the lower leg of Case 3 after a 3 months period antituberculosis therapy.

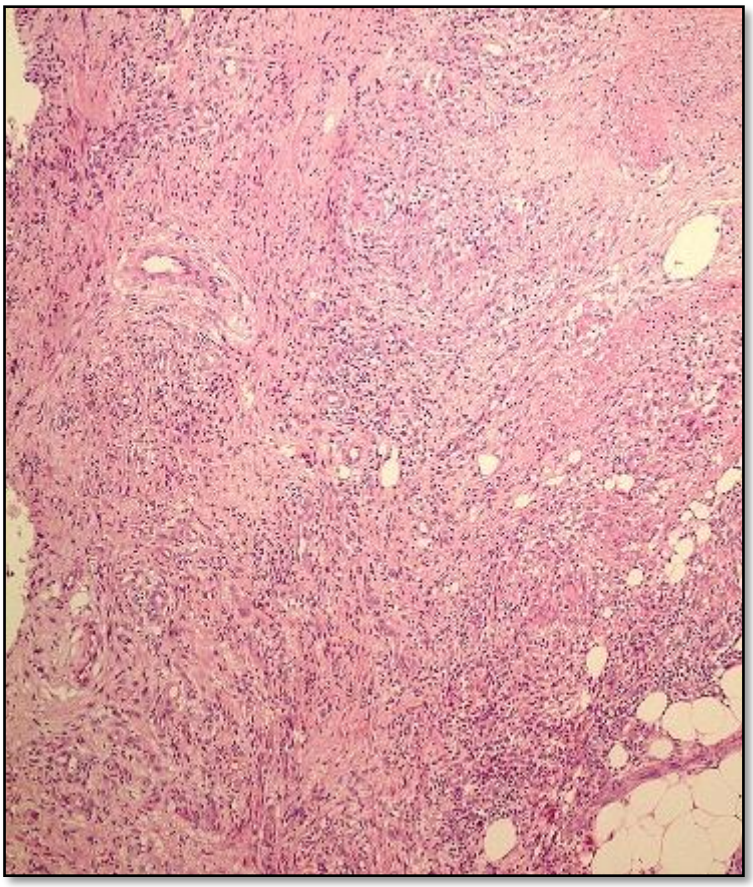

Figure 2. Lymphohisticytic infiltration and giant cells around the vessels which extend from dermis to subcutaneous adipose tissue forming granulomas. (HXE100)

Patient 2 was started on antituberculosis medication with 4- drug regimen, as well but he developed a drug eruption presenting with erythematous macules and papules on the 11th day of therapy. Since pyrazinamide was identified as the causative agent, it was replaced with moxifloxacin. After a 2- month period with 4- drug regimen, the treatment followed by dual therapy with rifampicin and isoniacid for additional 4-month.

DISCUSSION

Typical EIB is characterized by recurrent erythematous subcutaneous nodules and plaques on the posterior aspects of the lower legs. All 5 patients presented here had similar lesions on the anterior and posterior aspects of the lower legs, Case 1 and 2 had lesions on their arms, as well. Lesions on the arms have been reported rarely.[10] Dermatology textbooks typically describe EIB lesions as nodules which often ulcerate and discharge thus leave atrophic scars. [1] Although we have observed neither ulceration nor discharging, we still observed atrophic scars in three patients.

Erythrocyanosis, heavy column like calves, erythema surrounding follicular pores, and cutis marmorata are reported as frequently associated findings.[10] However, we did not observe any of these associated lesions. These observations show that the clinical picture of EIB may vary in a wide spectrum and clinicians in endemic countries should have an awareness of this rare manisfestation of latent infection with tuberculosis.

When the history of tuberculosis infection in the families of 4 patients in our series are considered, we propose that detailed questioning of the patients for either personal or family history for tuberculosis infection will be one of the most helpful hint for the diagnosis. It is also worth mentioning that all 4 patients discussed here did not mention their family history for tuberculosis at the first visit but later, only after pointed questioning due to the pathology results that they admitted their family history of tuberculosis. We believe that this tendency to keep tuberculosis history either personal or related to family private is a common practice in the Middle East where tuberculosis infection is still endemic. This may be an important obstacle in diagnosing the infection early and must be realized and handled by physicians.

Relevant clinical features, a positive TST, evidence of tuberculosis elsewhere in the body and histopathological findings are necessary for a diagnosis of EIB. The diagnosis can also be confirmed by the resolution of the lesions after anti-tuberculosis therapy. One of the striking diagnostic features is strongly positive TST which is usually larger than 20 mm.[11] Type III and/or type IV hypersensitivity reactions are suggested to play major roles in the etiopathogenesis of EIB and are belived to cause this exaggerated response to TST. [i] TST was applied in 3 of our 5 patients revealing positive results as 15 mm, 20 mm, and 25 mm. There are also reports suggesting the use of interferon-γ releasing assay test in the diagnosis of EIB. [13-15]

In recent years, the detection of *Mycobacterium tuberculosis* DNA from skin lesions by PCR has added new dimensions to the diagnosis of various forms tuberculosis infections as well as EIB. However, its role as a routine diagnostic test is uncertain. In a Spanish study of 74 specimens from patients with lobular granulomatous panniculitis (nodular vasculitis/EIB) PCR was positive in 54 % of the cases.[16] Schneider et al. [9] and Chen YH et al.[17] were able to detect mycobacterial DNA in 5 of 20 and 9 of 12 paraffin-embedded biopsy specimens of EIB,

respectively. In a study by Tan et al [18] 85 biopsy specimens representing different forms of cutaneous tuberculosis and tuberculids, 20 of them had the diagnosis of nodular vasculitis/erythema induratum. *Mycobacterium tuberculosis* DNA was not detected in any of specimens of nodular vasculitis/EI. In a study by Vieites et al. [19] an improved PCR analysis was applied to 65 patients with the diagnosis of EIB and 14% of the specimens was positive for mycobacterial DNA. PCR analysis was performed in 2 of our patients revealing positivity in one. This patient (Case 2) also had a positive interferon-γ releasing assay test, although she had no radiological findings associated with tuberculosis on chest- X ray examination

Whether antituberculosis treatment should be administered to every patient with EIB is controversial. Schneider et al. reported that 20 patients with EIB (only 5 of them had PCR positivity) had total clearance with three drug regimen.[9] In those patients with a strongly positive TST or positive PCR, a full course of 9 months of antituberculosis triple agent therapy is also recommended. [20,21] There are also reports of successful responses in patients treated with double drug regimen or isoniaside alone.[22] Additional helpful modalities such as supporting stockings, bed rest, treatment of venous insufficiency of the lower extremities, and nonsteroidal anti-inflammatory drugs are also suggested.[23] The published studies about the treatment of EIB are not controlled studies so the recommended treatments and responses to therapy were heterogenous for a definite conclusion. All four patients in our series who were treated with 4-drug regimen for 2 months followed by dual therapy for 4-months had complete resolution of their symptoms. However, case 1 who was treated with a 2- drug regimen experienced a recurrence which also resolved spontaneously.

CONCLUSION

In this series we wanted to summarize our experience with EID, by means of 5 new patients that we diagnosed and treated during last year and draw attention to the mostly overlooked manifestation of latent tuberculosis.

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