OMCR

Oxford Medical Case Reports, 2017;8, 147–149

doi: 10.1093/omcr/omx041
Case Report

CASE REPORT

Erythema nodosum as sign of primary tuberculosis

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Abstract

Erythema nodosum is a panniculitis associated with numerous diseases such as infections, inflammatory diseases, tuberculosis or can be idiopathic. We here report a case of a woman with erythema nodosum and reactive arthritis who was subsequently diagnosed with tuberculosis. A high level of suspicion and a thorough clinical and laboratory investigation of the patient presenting with erythema nodosum is required, in order to detect a possible systemic underlying condition.

BACKGROUND

Erythema nodosum is a skin condition where red lumps appear on the shins and less commonly forearms and thighs. This is a painful disorder of the subcutaneous fat that can manifest with tender, erythematous, subcutaneous nodules.

Generally, it is idiopathic (up to 55% of the cases), but it has also been associated with numerous diseases; most commonly streptococcal pharyngitis especially in children (up to 48%) [1]. Often it may be the first sign of a systemic disease such as tuberculosis, bacterial or deep fungal infection, sarcoidosis (11–25%), inflammatory bowel disease or associated with pregnancy (2–5%) [2, 3]. Drugs (3–15%), including oral contraceptives and some antibiotics (sulphonamides, amoxicillin), and hormonal reactions are other identifiable causes in the adult population. Other more rare causes are viral infections (HIV, EBV, Herpes, hepatitis B and C), syphilis, parasitic infections (Amoebiasis, giardiasis) and lymphoma and other malignancies [3]. Many of the underlying causes are treatable emphasizing the need of fully investigating possible triggers.

A prodrome commonly occurs as early as one to three weeks before the onset of erythema nodosum, regardless of the aetiology. Specific symptoms may include weight loss, malaise, low-grade fever, cough and arthralgia with or without arthritis. Coexistence between arthritis and erythema nodosum has been described due to *Yersinia enterocolitica* [4], Loffler' syndrome [5], although this has also been described in the coexistence between reactive arthritis and tuberculosis (Poncet's disease) [6].

Therefore, when a patient with erythema nodosum is seen in primary care it is important for the diagnostic evaluation to consider a broad differential diagnosis.

We describe a case of a young woman with symmetrical ankle arthritis and erythema nodosum associated with a strong positive tuberculin skin test (TST) but no detectable focus of tubercular infection treated as latent TB with successful resolution of the symptoms.

CASE REPORT

A 22-year-old woman of Indian origin presented to our outpatient clinic with painful ankle swelling which had started 24 h earlier. This was preceded by a painful, erythematous rash consisting of three nodules, one located on the anterior surface of her right tibia, and the remaining two on her left tibia, 10 days prior to the onset of ankle swelling. The patient did not report any other symptoms as fever, fatigue, malaise, weight loss, dysuria and cough. There was no significant past medical history. She was not taking any prescribed or over the counter medication.

On examination, cardiovascular and respiratory examination was normal. There was no lymphadenopathy or hepatosplenomegaly. Both ankles were red, hot, swollen and there was limitation in movements. The nodules were poorly demarcated, 2–4 cm in diameter and they were erythematous and painful (Fig. 1).

Laboratory tests revealed a normal blood count except for a mild microcytic hypochromic anaemia (Hb 10.4 g/dl (normal

Received: March 19, 2017. **Revised:** June 3, 2017. **Accepted:** July 29, 2017

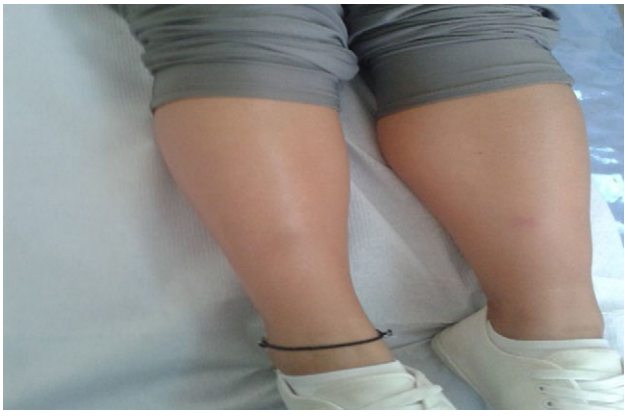

Figure 1: Bilateral erythema nodosum, indicated here with blue arrows.

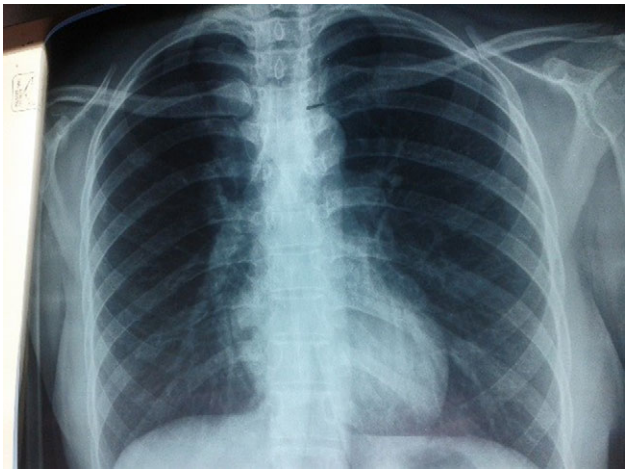

Figure 2: Chest radiograph of our patient revealed no abnormality.

range 12–16 g/dl), Hct 33.6% (normal range: 37–47%), iron 51 μg/dl (normal range 50–175) and ferritin 14 ng/ml (normal range: 15–150)). Erythrocyte sedimentation rate (ESR) was 30 mm at the first hour. AST, ALT, CRP, rheumatoid factor and ASTO titre were normal. Thyroid function tests (FT3, FT4, TSH) were within normal range. Autoantibodies (rheumatoid factor, anti-DNA) were negative. Chest radiography was normal (Fig. 2). The patient had a TST, and was given a non-steroidal anti-inflammatory drug (meloxicam) for her arthritis and was advised to return in 72 h for re-evaluation. Upon her return, the arthritis had improved and TST reaction was 24 mm with blistering (positive > 15 mm in patients without risk factors) [7].

In this clinical context, reactive arthritis and erythema nodosum likely due to tuberculosis was diagnosed and patient was referred to the respiratory clinic for further evaluation and management. Screening of individuals who came into close contact with our patient was also organized. Our patient's father also had a positive TST and was referred to the respiratory clinic as well for further evaluation.

Our patient had a normal thoracic CT scan and a negative Ziehl–Nielsen test for mycobacteria. She also had a negative Lowenstein–Jensen culture. The diagnosis of TB infection was considered despite the lack of detectable focus of tubercular infection. The patient was commenced a combination of antituberculous medication (2 months of isoniazid/rifampicin/pyrazinamide/ethambutol followed by 4 months of isoniazid/rifampicin) and was advised to return for monthly evaluation in our clinic. At her first visit the rash had completely disappeared and arthritis had resolved.

DISCUSSION

Erythema nodosum is a well-known delayed hypersensitivity reaction to a variety of different stimuli such as infections, autoimmune diseases or drugs, depending on the country of the patient's origin. Its incidence is ~1–5 per 100 000 persons with almost half of the cases reported being idiopathic, indicating that possibly one in two cases could be secondary to a systemic condition or medication.

The association of erythema nodosum with tuberculosis is well known, especially in endemic regions [3, 8]. Some series reported TB as the second most common cause of secondary erythema nodosum [9], whereas others consider Mycobacterium tuberculosis infection as a rare cause [10]. This reflects differences in TB incidence across the world. A recent Chinese study showed that almost all patients with primary TB presented with EN whereas 20% of those with EN had tuberculosis [11]. More strikingly, recent data from Denmark showed a strong association of EN with TB diagnosis within one month of diagnosis [8]. Almost 50% of cases with positive interferon-gamma release assay in keeping with mycobacterium TB infection and EN were subsequently given a diagnosis of active TB. The study concludes that either EN is a strong predictor of TB or an early symptom of primary extra-pulmonary TB and certainly warrants thorough assessment and close follow-up.

Similarly, Mert *et al.*, reported that among clinical forms of TB, primary TB is unique to cause erythema nodosum, frequently seen in children and young adolescents. It may even manifest before the development of a skin-test reaction to tuberculin [9]. On the other hand, erythema nodosum has also been described in patients with markedly positive TST reactions in the absence of any detectable focus of TB infection.

For these reasons, all patients with erythema nodosum should be stratified by risk for tuberculosis exposure. Investigations should include TST, chest radiography and acid-fast bacilli sputum analysis [9].

Reactive arthritis and *Mycobacterium tuberculosis* is a rare presentation of TB and sometimes reported in bibliography as Poncet's disease [12]. The association of reactive arthritis, erythema nodosum and *M. tuberculosis* is even more rare and reported only in cases reports. In our case arthritis of the ankles was diagnosed clinically (painful, warm joints with restriction in motion which reversed quickly after the initiation of therapy) although joint aspiration and synovial fluid analysis would have been the preferred method to demonstrate the aseptic reactive nature of the arthritis.

When it comes to treatment strategy there is an ongoing discussion on whether the demonstration of MTI and EN should be treated as active TB (combination schemes) or as latent TB with preventive monotherapy.

On one hand, WHO guidelines emphasize the need to exclude TB before choosing preventive monotherapy [13].

On the other hand, experts argue that antitubercular therapy should be initiated for EN in patients with positive TST reactions with or without a positively identified focus of infection [14]. It is suggested that in individuals with highly positive Tuberculin test there is likely to be a small focus of infection somewhere in the body not identified by the routine diagnostic tests and any delay in treatment might facilitate progress and involvement of other organs [14]. This is particularly important

in patients with accompanied reactive arthritis, a rare complication of TB described a Poncet's disease, with fast resolution of symptoms after initiation of therapy. In our case the origins of the patient from an endemic TB region, the combination of EN with possible reactive arthritis and the strong positive TST prompted to initiation of TB therapy with rapid resolution of the clinical symptoms (Figs 1 and 2).

CONCLUSION

The manifestation of erythema nodosum secondary to TB infection remains a challenge for health professionals as correct diagnosis of the primary aetiology has important therapeutic implications for the patients and screening for close contacts. HIV rise, poor standards of living and migration from endemic areas have changed the epidemiology of TB in the last 2 decades in both developing and developed countries and should prompt clinicians to exclude TB as the underlying cause in all cases of erythema nodosum.

CONFLICT OF INTEREST STATEMENT

None declared.

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