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Case Report

Prurigo nodularis due to *Mycobacterium tuberculosis*

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Prurigo nodularis (PN) is a rare chronic skin disorder of unknown origin. Here we describe what is believed to be the first case of PN associated with tuberculosis. For the first time, culture and PCR analysis of skin biopsy confirmed the presence of *Mycobacterium tuberculosis* complex in PN skin lesions. The pruritus and skin lesions resolved following antitubercular therapy. Our case provides further evidence in favour of a link between PN and mycobacterial infection.

Introduction

Prurigo nodularis (PN) is a chronic skin disorder characterized by intensely pruritic papulonodular lesions that mainly appear on the extensor surfaces of the limbs. The disease is relatively rare and can occur at any age, but it is more commonly reported in middle-aged women. The definition and pathogenesis of PN are somewhat confusing. It is described as being associated with a number of disorders. Numerous infectious agents (bacterial and viral) have been suggested as possible triggers. Although several studies have provided important information linking infectious agents to PN, strong evidence for a direct casual association between such infections and PN is still lacking (Mattila *et al.*, 1996; Neri *et al.*, 1998, 1999; Alfadley *et al.*, 2003; Loffeld & Tan, 2004).

In some cases PN would appear to be the direct result of skin infection, with the infectious organisms identifiable in skin lesions, while in others (e.g. human immunodeficiency virus and viral hepatitis) the lesions are apparently immune-system mediated (Lee & Shumack, 2005; Accioly-Filho *et al.*, 2000). These observations suggest that it is simply a common skin response to a variety of insults. PN is consequently a difficult condition to treat and identifying a treatment strategy can be challenging. To contribute to a better understanding of this skin disorder, we report for what is believed to be the first time a case of PN linked with *Mycobacterium tuberculosis* complex (MTBC) infection in a patient with pulmonary tuberculosis.

Case report

In July 2007, a 30-year-old man of Ghanaian origin came to the Emergency Department of Policlinico 'Paolo Giaccone' University Hospital, Palermo, Italy, with fever and chest pain that he had been experiencing for 3 weeks. The patient had lived in Italy for 5 years. A review of his medical history revealed no signs of previous chronic diseases. A human immunodeficiency virus test performed on admission was negative.

At the time of admission, the patient was febrile (38.3 °C), and complained of a productive cough and chest pain in his left side. He was also experiencing intense itching in his upper and lower limbs. On chest auscultation, localized crackles and wheezing were heard in the left upper zone. Further examination revealed nodular skin lesions 0.5–1.5 cm in diameter, mainly on his upper and lower limbs. The lesions were hard, hyperpigmented nodules, with a smooth surface. Some of these nodules showed scratch injury. The skin between the lesions was normal (Fig. 1). The patient had suffered from these lesions for 15 months.

Laboratory tests revealed: a white blood cell count of 4180 cells mm^{-3}, with 49.3 % neutrophils, 27.5 % lymphocytes, 20.6 % monocytes and 1.9 % eosinophils; a haemoglobin level of 11.7 g dl^{-1}; a platelet count of 145 000 cells mm^{-3}; an aspartate aminotransferase level of 67 IU l^{-1} and an alanine aminotransferase level of 39 IU l^{-1}. Serum protein electrophoresis revealed a slightly low level of albumin (3.36 g dl^{-1}, normal range 3.48–5.39 g dl^{-1}) with polyclonal hypergammaglobulinaemia (2.29 g dl^{-1}, normal range 0.67–1.56 g dl^{-1}). His blood glucose level, serum electrolyte concentrations and renal function test results were within normal limits.

A chest X-ray showed a bilateral parenchymal hilar and peri-hilar consolidation, with marked interstitial bronchovascular fibrosis and bronchiectasiae in the left lung. Thoracic computed tomography images confirmed the presence of multiple bilateral areas of air space consolidation with small nodular lesions and cavitation. Fibrocalcific

Abbreviations: EIB, erythema induratum of Bazin; MTBC, *Mycobacterium tuberculosis* complex; PN, prurigo nodularis.

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Fig. 1. Hyperpigmented nodular lesions on the flexor surface of the right forearm.

nodules were present in the upper region of the left lung. Hilar-mediastinal lymphadenopathy was also detected.

The patient had a positive Mantoux skin test reaction (12 mm in duration after 48 h). Acid-fast bacilli were detected in a Ziehl–Neelsen-stained sputum smear. PCR based on the amplification of the IS*6110* insertion sequence, followed by a hybridization step, was carried out on the sputum sample and yielded a positive result for MTBC (Forbes & Hicks, 1993). Sputum culture on Lowenstein–Jensen medium was positive for acid-fast bacilli that were identified as MTBC based on cultural characteristics and biochemical tests (Roberts *et al.*, 1991), and on RFLP of the *rpoB* gene (Lee *et al.*, 2000).

Pulmonary tuberculosis was diagnosed and the patient was treated with quadruple therapy (rifampicin, isoniazid, pyrazinamide and ethambutol) until susceptibility testing results were available. Three weeks later, the result of susceptibility test showed resistance to ethambutol. Due to the patient's poor compliance we decided to protract the quadruple therapy, replacing ethambutol with intramuscular streptomycin for 30 days.

Six days after initiating antitubercular therapy a biopsy of one of the nodules on the forearm was performed. A clinical diagnosis of PN was made on the basis of cutaneous features. An antihistaminic drug was administered for 15 days without any remission of symptoms.

Histological examination of the biopsy specimen showed hyperparakeratosis, hypergranulosis (i.e. thickening of the stratum granulosum) and acanthosis. Papillary dermal sclerosis due to fibroblast hyperplasia along with a scant perivascular lymphocytic infiltrate were also present; the subcutaneous fat was not involved and no specific changes related to tuberculosis were observed. These findings confirmed the clinical suspicion of PN.

A fragment of the fresh biopsy sample was also examined for the presence of mycobacteria. Ziehl–Neelsen staining was negative. IS*6110*-PCR was carried out after extraction of DNA using a protocol based upon incubation steps with SDS and proteinase K, a phenol/chloroform extraction and an RNase treatment. Checking for contaminant DNA was performed using PCR amplification of a blank extract and the PCR reagent mix. PCR yielded a positive result for MTBC (Forbes & Hicks, 1993). Culture on Lowenstein–Jensen medium was also positive for MTBC. Reported methods were used to identify tubercle bacilli on colonies obtained from cutaneous specimens (Roberts *et al.*, 1991; Lee *et al.*, 2000).

Haematochemical parameters and sputum smears were examined monthly. The only remarkable alteration was seen in eosinophil number. This count was initially normal ($<$300 cells mm^{-3}) but increased 2 weeks after admission, reaching a peak of 579 cells mm^{-3} 1 month later.

About 40 days after beginning antitubercular therapy, the patient reported an improvement in pruritus. After 2 months of treatment, a sputum smear was negative, and the patient was discharged and referred for outpatient follow up. At that time, the pruritus had disappeared and the nodular lesions were still present though reduced in size.

During the follow up, MTBC continued to be undetectable in sputum samples examined with Ziehl–Neelsen staining, and PCR was negative after 4 months of antitubercular treatment. At that time, only a few small, non-itchy lesions were still detectable on the patient's limbs; his eosinophil count was within the normal range. The patient completed a standard 6 month course of antitubercular therapy.

Discussion

PN is one of the most challenging of all chronic skin disorders in terms of establishing its aetiology and determining treatment strategies (Accioly-Filho *et al.*, 2000; Alfadley *et al.*, 2003). These issues are related to what triggers it, as an important first step in therapy is to identify the underlying cause and treat the condition accordingly. Mattila *et al.* (1996) described six patients affected by PN due to mycobacteria other than tuberculosis, identified by culture of skin biopsy specimens. Two of these patients had a good response to treatment with antitubercular drugs.

PN is a distinctive condition and its diagnosis is mainly clinical (Accioly-Filho *et al.*, 2000). For our patient, a diagnosis of PN was made based on skin manifestations and an intense itching that had led to the lesions rapidly becoming excoriated or crusted.

Clinical and instrumental assessment associated with the results of bacterial isolation from the lesions and the early improvement of our patient's symptoms following standard antitubercular therapy prompted us to assert that this was, to the best of our knowledge, the first reported case of PN linked to MTBC. Indeed, a relapse of skin lesions

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occurred during the active tuberculosis infection, and improvement was evident after 40 days of effective antitubercular therapy. Interestingly, the clinical remission of skin lesions coincided with the negativization of microbiological markers of systemic infection.

In the differential diagnosis of our patient we considered erythema induratum of Bazin (EIB), also called tuberculids. EIB is a subcutaneous panniculitis and vasculitis, which occurs mainly on the lower extremities of middle-aged women with signs of vascular insufficiency. Like other forms of cutaneous tuberculosis, it is considered to be a hypersensitivity immune reaction to MTBC and biopsy culture is always negative. Similar to our patient, symptoms associated with EIB can improve with antitubercular therapy (Mascaró & Baselga, 2008; Segura *et al.*, 2008). Nevertheless, unlike in our patient's case, EIB lesions are not pruritic but painful, and the nodules are confluent and erythematic, whereas in PN lesions the nodules are rarely erythematic and, when erythema is reported, it is in a precocious phase as the nodules rapidly become pigmented (Accioly-Filho *et al.*, 2000). Furthermore, histological examination of biopsy specimens obtained from our patient did not reveal any of the typical features described in patients with EIB, but rather showed the characteristic changes in epidermis and derma consistent with PN (Segura *et al.*, 2008; Lee & Shumack, 2005; Mobini *et al.*, 2005).

It has been suggested that eosinophils play a pathogenic role in PN (Accioly-Filho *et al.*, 2000; Tanaka *et al.*, 1995). In our patient, the number of circulating eosinophils increased during the course of antitubercular therapy. Conversely, there was no increase in number of eosinophils in the affected skin. We assumed that blood eosinophilia was a drug-induced side effect, as reported by Wong *et al.* (1995).

Cutaneous tuberculosis can be acquired either exogenously (directly through injured skin) or endogenously (spreading from other organs). Skin trauma due to scratching easily introduces pathogens into the skin. However, in our case the positive response to antitubercular therapy suggested that *M. tuberculosis* spreading from the pulmonary infection might have been the primary cause of the skin disorder.

These findings suggest the need to consider a tubercular aetiology for atypical chronic skin manifestations such as PN, especially in patients coming from tuberculosis-endemic countries, as systemic infection could be concomitant. Early diagnosis could prevent the development of a more severe clinical picture.

In conclusion, this is believed to be the first documented report of PN due to MTBC. Two recommendations arise from our case: (i) it is opportune to consider PN as one of the various patterns of cutaneous tuberculosis; (ii) it is important to carry out specific microbiological investigations for MTBC (e.g. PCR and/or culture) combined with histopathological analysis of PN lesions in patients with risk factors associated with latent or active tuberculosis.

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