

Recurrence of erythema induratum of Bazin in a patient under chemotherapy for breast cancer

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SUMMARY

Erythema induratum of Bazin (EIB) is a chronic nodular eruption occurring on the lower legs of young and middle-aged women which is considered the most common tuberculid. A 54-year-old woman, in treatment with chemotherapy for breast cancer, presented subcutaneous erythematous plaques and nodules on the lower limbs. She had been diagnosed with EIB 3 years earlier and diagnostic work-up showed at that time signs suggestive of latent tuberculosis. The suspect of a recurrent form of EIB was confirmed by histopathological examination. A peculiar feature of our report consists in the recurrence of EIB, which is regarded as a hyperergic response against *M. tuberculosis* antigens, in a patient who was receiving chemotherapy with well-known immunosuppressive effects.

KEY WORDS: Erythema induratum of Bazin, Tuberculosis, Tuberculid, *Mycobacterium tuberculosis*, Cancer chemotherapy

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In late 2009 a 54-year-old woman requested our consultation for a 1-month history of painful violaceous subcutaneous nodules located on the posterior and lateral aspects of the legs. Similar manifestations had already occurred 3 years earlier, some months after tuberculosis (TB) was diagnosed in close relatives, in particular pulmonary TB in her husband and tubercular meningitis in her son. At that time, chest x-ray examination revealed fibrotic lesions in the right lung upper lobe.

A purified protein derivative of tuberculin (PPD) skin test was strongly positive with erythema and induration of 25 mm after 48 hours. Sputum, stool and urine cultures were negative. Therefore, a biopsy was taken from the lesional skin and histopathology revealed a lobular neutrophilic and granulomatous panniculitis with fibrin deposition within the wall of small vessels. Based on

the clinical, laboratory and histopathological findings, the diagnosis of erythema induratum of Bazin (EIB) was made.

The patient was referred to an infectivologist who did not prescribe any specific treatment on that occasion, because of the tendency towards a spontaneous improvement of skin lesions, in the absence of any signs indicating an active TB infection.

The patient did not show any major changes in her clinical conditions until the beginning of 2009, when breast cancer was diagnosed, and she was treated with radical mastectomy and axillary lymph node dissection and then underwent a 6-month chemotherapy regimen with cyclophosphamide, methotrexate and 5-fluorouracil.

Soon before the administration of the 6th cycle, the patient noted the reappearance of the formerly described lesions on the lower extremities. On physical examination performed at the end of the chemotherapy regimen, sparse firm and deep red-violaceous subcutaneous nodules and indurated plaques were present on the posterior and lateral aspects of the lower extremities.

Ulceration was absent and there were a few hyperpigmented scars and atrophic lesions, sec-

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ondary to healing of preexisting lesions. Signs of chronic venous stasis were also evident. Histopathological analysis revealed again features suggestive of EIB.

Chest x-ray confirmed the presence of the fibrotic lesions already seen 3 years before. The PPD testing demonstrated an erythematous induration of 10 mm at 48 hours. A QuantiFERON-TB Gold test was positive. Polymerase chain reaction (PCR) studies for *Mycobacterium tuberculosis* on lesional tissue, as well as on urine, sputum and stool samples, failed to isolate *M. tuberculosis* DNA. High-resolution computed tomography scanning of the chest showed calcification nodules in the upper right lobe with ipsilateral hilar lymph node calcification.

Within two months after the end of chemotherapy, no new skin lesions occurred and a major clinical improvement of the preexisting lesions was observed. In agreement with the pneumologist's suggestions, the patient received anti-TB chemoprophylaxis with rifampicin and isoniazid for 3 months, which induced a complete remission of EIB.

EIB is a chronic, nodular eruption that usually occurs on the lower legs of middle-aged women and is considered the most common tuberculid. The etiopathogenesis of the disease is still controversial, as also is its association with TB infection, and some authors theorize EIB as being a multifactorial disorder with TB included among the many different causes (Mascarò *et al.*, 2008). If untreated, the disease is generally chronic with recurrent crops of new elements arising over a period of many years (Requena *et al.*, 2001) (Mascarò *et al.*, 2008). The course and the activity of EIB may fluctuate based on the underlying immune status of the patient.

This report concerns a case of EIB in the setting of a presumed latent TB infection. The patient had a recurrence of EIB lesions, which initially developed 3 years earlier, after the administration of chemotherapy for breast cancer. The reappearance of EIB seems to be somehow peculiar in such a clinical context, given the immunosuppressive effects of chemotherapy. In fact, as a tuberculid, EIB is regarded as a cell-mediated hypersensitivity reaction against disseminated *M. tuberculosis* or its antigens, in patients with a moderate to high degree of immunity (Leow *et al.*, 2006) (Yen *et al.*, 1997). Of note, the reaction

to the tuberculin skin test in our patient was notably weaker on the latter occasion compared to that observed during the first EIB episode, and this finding might be due to the suppressive influence of cancer chemotherapy on the immune response.

However, such an influence was not complete considering the ability to boost a cell-mediated hypersensitivity response like that responsible for recurrence of EIB. In this respect, it should be mentioned that cyclophosphamide, which was a component of the chemotherapeutic regimen in our patient, has ambivalent effects on immune function and is also capable of enhancing delayed-type hypersensitivity reactions (Brode *et al.*, 2008).

The widely accepted criteria we used to diagnose EIB in our patient were: circumstantial evidence of TB exposure, clinical morphology, histopathological features, and positive tuberculin skin test (Barbagallo *et al.*, 2002). The clinical relevance of PCR on lesional tissue is still under investigation and currently remains unknown (Tan *et al.*, 2001) (Hsiao *et al.*, 2003).

QuantiFERON-TB Gold test may be useful, particularly in some circumstances, e.g., in BCG-vaccinated subjects.

Despite the absence of proven TB infection in EIB, anti-TB therapy with rifampicin, isoniazid, pyrazinamide and ethambutol has been shown to be effective (Schneider *et al.*, 1995) (Alothman *et al.*, 2007). However, considering the risk of serious side effects, anti-TB therapy is generally reserved to patients who show a strongly positive reaction to the tuberculin skin test or when *M. tuberculosis* DNA is detected by PCR and/or the mycobacterium is isolated from cultures.

Other measures, such as rest, compression bandages and non-steroidal anti-inflammatory agents, may alleviate symptoms and improve lesions.

In our case, an intermediate option was chosen represented by anti-TB chemoprophylaxis, considering the inability to identify mycobacterial DNA and any active infectious focus, the tendency towards a spontaneous clinical improvement, as well as completion of the chemotherapy regimen. This prophylaxis was also scheduled as a preventive measure to avoid reactivation of a latent TB focus, also in perspective of possible future use of further cancer chemotherapy if required.

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