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# Atypical CD30+ Cutaneous Lymphoid Proliferation in a Patient With Tuberculosis Infection

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**Abstract:** We describe the case of a 65-year-old woman affected by a diffuse lymphadenopathy consistent with tuberculous infection who developed a papular eruption on the head and neck region. Histopathologic examination of one papule showed an atypical CD30+ lymphoid infiltrate, which initially was cause of concern for the pathologists but was eventually regarded as reactive in nature. The case reported herein enlarges the spectrum of inflammatory infiltrates in which atypical CD30+ cells may be found. Since the reactive atypical CD30+ cells are morphologically similar to those cells observed in CD30+ lymphoproliferative disorders, including lymphomatoid papulosis, complete clinical history and laboratory findings are necessary to make the final and correct diagnosis. Although the pathogenetic relevance of the presence of CD30+ cells within the cutaneous infiltrate of patients with systemic tuberculosis remains to be determined, our findings support the hypothesis that the cytokine profile associated with tuberculosis may not be strictly T<sub>H</sub>1-like, and that a T<sub>H</sub>1-like to T<sub>H</sub>2-like switch may also occur.

**Key Words:** CD30, Cytokines, Pseudolymphoma, Tuberculid, Tuberculosis

(*Am J Dermatopathol* 2004;26:234–236)

**T**uberculosis (TBC) may rarely involve the skin, featuring a wide spectrum of clinicopathologic entities that are generally classified according to time of infection (primary versus secondary), presumed route of infection, and clinical appearance. In particular, lupus vulgaris is the most common form of TBC reinfection, affecting primarily the head and neck region of young patients. The usual clinical picture is with multiple erythematous papules forming a plaque, which on diascopy shows small “apple jelly” nodules. Histopathologically, there are confluent granulomas surrounded by variable mantles of lymphocytes; central caseation necrosis and Langhans giant cells are sometimes present. Tuberculids are a heterogeneous

group of cutaneous lesions that occur in association with TBC infection in patients with a high degree of immunity and allergic sensitivity to the organism.

We herein describe the case of a 65-year-old woman affected by a diffuse lymphadenopathy consistent with tuberculosis who developed a papular eruption on the head and neck region. Histopathologic examination of one papule showed an atypical CD30+ lymphoid infiltrate that initially was cause of concern for the pathologists, but was eventually regarded as reactive. The true nature and the possible pathogenetic significance of the peculiar picture observed are discussed.

## CASE REPORT

A 65-year-old woman presented with a diffuse lymphadenopathy, involving the cervical and left axillary lymph nodes, associated with night sweats, weight loss, and weakness. A computed tomography scan demonstrated also the presence of enlarged mediastinal lymph nodes, whereas chest radiographs failed to show lung infiltration. The left axillary lymph node was surgically excised. Histopathologic examination revealed the presence of multiple epithelioid granulomas surrounded by mantles of lymphocytes and not associated with significant caseous necrosis. The histopathologic findings were considered consistent with a diagnosis of lymph node TBC. A Ziehl-Neelsen stain was negative. A nested polymerase chain reaction assay for amplification of *Mycobacterium tuberculosis* DNA and immunohistochemical analysis for B124 antibody raised against *Mycobacterium bovis* were negative. Shortly after, the patient developed multiple cutaneous papules located on the head and neck region measuring approximately 3 to 4 mm in diameter (Fig. 1). The papules did not coalesce and did not show spontaneous regression. Histopathologic examination of one papule located on the temporal region demonstrated a dense atypical lymphoid infiltrate composed predominantly of large pleomorphic lymphocytes with rare, small, round lymphocytes within the superficial and middle dermis (Fig. 2A). The large hyperchromatic cells showed an irregular nuclear contour and irregular chromatin distribution. Some of the cells had prominent large nucleoli (Fig. 2B). Numerous mitotic figures were observed. Immunohistochemical analysis demonstrated diffuse CD3 expression. CD30 was expressed in approximately 30% of the infiltrate and in almost all large lymphocytes (Fig. 2C). Numerous CD68+ histiocytes were present, although well organized

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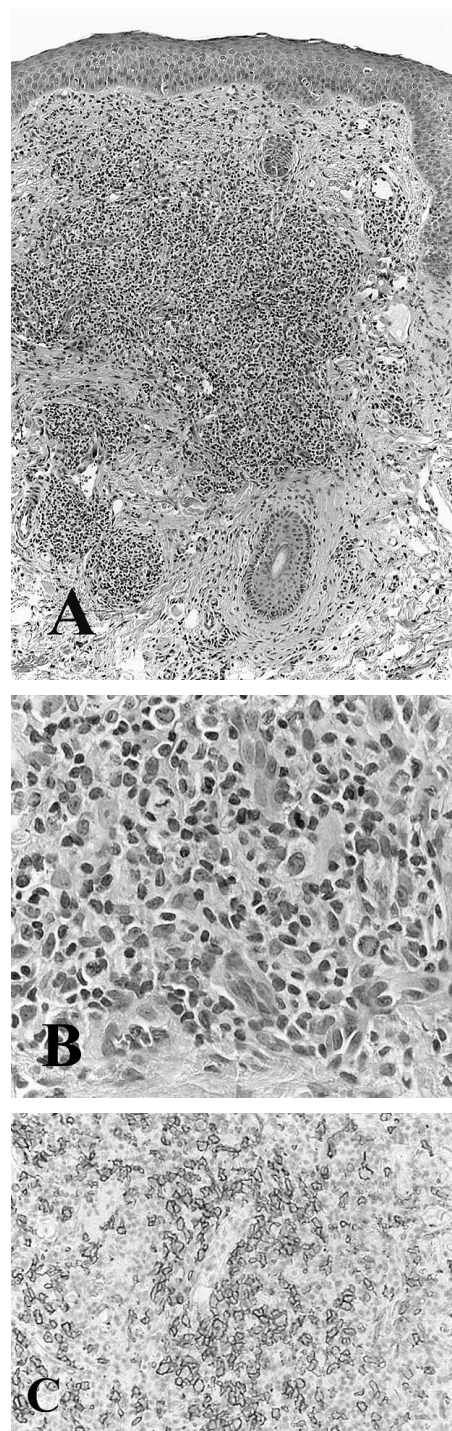


**FIGURE 1.** Multiple cutaneous papules measuring approximately 3 to 4 mm in diameter located on the head region.

granulomas were not detected. The B-cell marker CD20 stained less than 5% of the cells. The proliferation marker Mib-1 was expressed in approximately 80% of lymphoid cells. T-cell receptor rearrangement was negative. A second skin biopsy was performed on another papule. Histopathologically, a non-necrotizing granulomatous dermatitis with variable numbers of giant cells was observed. A CD30 stain was negative. The immunologic profile on peripheral blood revealed that the percentage of CD4<sup>+</sup>/CD30<sup>+</sup> was only 0.2%. A Mantoux test, with the intradermal injection of 5 TU PPD-S, showed an induration of 30 mm after 48 to 72 hours, strongly supporting a diagnosis of TBC. Polymerase chain reaction identification of *Mycobacterium tuberculosis*, performed on microbiologic cultures of a cutaneous sample, was negative. Upon diagnosis, the patient was given antitubercular therapy consisting of rifampicin (600 mg qd), isoniazid (300 mg qd), ethambutol (500 mg bid), and pyrazinamide (500 mg bid) daily for 2 months, followed by 2 drugs (rifampicin and isoniazid) for 6 months. The therapy led to a significant reduction of lymph node swellings, whereas the cutaneous lesions ran a more prolonged course and cleared completely after 12 months. Neither complications nor drug-dependent side effects occurred.

## DISCUSSION

Although available histopathologic and molecular data do not allow to definitively establish that in the current case the lymph node and skin lesions were due to TBC infection, the results of the Mantoux reaction and of the second skin biopsy, along with the resolution of the lymph node and cutaneous lesions upon antitubercular therapy, were highly suggestive for TBC. Indeed, it is known that suboptimal fixation combined with a very low amount of mycobacteria in the tissue sample may lead to a false negative result of the polymerase chain reaction from formalin-fixed, paraffin-embedded tissue. The open issue is why apparently similar cutaneous lesions showed different histopathologic features. In particular, it is debatable whether the peculiar picture observed in the first skin biopsy may, in this clinical setting, be classified as a form of tuberculid, since this concept has been challenged from time to time



**FIGURE 2.** (A) Histopathologic examination showed a dense atypical lymphoid infiltrate composed predominantly of large pleomorphic lymphocytes with rare smaller lymphocytes within the superficial and middle dermis. (B) The atypical pleomorphic cells showed an irregular nuclear contour, irregular chromatin distribution, and prominent large nucleoli. (C) CD30 strong immunoreactivity was observed in the large pleomorphic lymphocytes.



and since it is not yet clear which clinicopathologic entities can be classified under this term. On clinical grounds, the papular eruption was reminiscent of so-called "lupus miliaris disseminatus faciei," originally thought to be a variant of lupus vulgaris or a tuberculid due to its histopathologic similarity with TBC. However, the terminology, pathogenesis, and the association of lupus miliaris disseminatus faciei with TBC have been recently questioned.<sup>1</sup>

In the current case, we were concerned by the presence in the first skin biopsy of large, atypical CD30+ pleomorphic lymphocytes within the dermis. Although a CD30+ cutaneous lymphoproliferative lesion, in particular, lymphomatoid papulosis, was initially considered, clinical features (absence of necrosis and ulceration, crusting, and spontaneous regression) and laboratory findings supported the reactive nature of the infiltrate. Conversely, the absence of T-cell receptor gene rearrangement did not per se rule out lymphomatoid papulosis.

On histopathologic examination, the differential diagnosis of an atypical CD30+ lymphoid proliferation is broad and includes primary cutaneous CD30+ T-cell lymphoproliferative disorders (including lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma, and borderline lesions) and reactive infiltrates in response to pharmaceutical agents (such as carbamazepine) or viral infections (especially herpes virus, human papillomavirus, and Epstein-Barr virus infections).<sup>2,3</sup> As rule, only a minority of the infiltrate in non-neoplastic conditions is CD30+, and rarely is there clustering of the CD30+ lymphoid population. Among inflammatory conditions of the skin, atypical CD30+ lymphocytes have been described in rare cases of atopic dermatitis,<sup>4</sup> molluscum contagiosum,<sup>5</sup> and recently, in association with a delayed skin reaction to coelenterates.<sup>6</sup>

CD30 is a member of the tumor necrosis/nerve growth factor receptor superfamily, originally described as a marker for Hodgkin and Reed-Sternberg cells in Hodgkin disease, but subsequently found on various non-Hodgkin lymphomas and on activated T and B cells.<sup>7,8</sup> Moreover, CD30 is consistently expressed by human CD4<sup>+</sup> T<sub>H</sub>2 and T<sub>H</sub>0 and CD8<sup>+</sup> type 2 cytotoxic T-cell clones, whereas CD4<sup>+</sup> T<sub>H</sub>1 and CD8<sup>+</sup> type 1 cytotoxic clones usually exhibit poor or no CD30 expression.<sup>9</sup> Therefore, the CD30 molecule is generally regarded as a putative specific marker of inflammatory infiltrates with a T<sub>H</sub>2-type cytokine pattern.

In the pathogenesis of human TBC, whether strict T<sub>H</sub>1-like (type 1) or T<sub>H</sub>2-like (type 2) cytokine profiles occur is still a controversial issue. The dominant view has been that there is little or no activation of T<sub>H</sub>2-like cytokine production in human TBC. However, a series of publications have demonstrated that there might be an inappropriate T<sub>H</sub>2-like component in many affected patients.<sup>10-12</sup> It has also been suggested that cytokine profiles in mycobacterial diseases may vary according to different anatomic sites and depending on the severity of the disease.<sup>13</sup> In line with our observations, increased

CD30 expression by *Mycobacterium tuberculosis*-stimulated  $\alpha/\beta$  and  $\gamma/\delta$  T cells and elevated numbers of CD30+  $\alpha/\beta$  T cells have been demonstrated in TBC pleuritis and affected lung tissue.<sup>14</sup> Taken together, these results indicate that *Mycobacterium tuberculosis* is a potent inducer of CD30 expression in T<sub>H</sub>1-like cells and argue against the exclusive correlation of CD30 expression with T<sub>H</sub>2-like cell responses.

In conclusion, the present case enlarges the spectrum of inflammatory infiltrates in which atypical CD30+ cells may be found. Since the reactive atypical CD30+ cells are morphologically similar to those cells observed in CD30+ lymphoproliferative disorders, including lymphomatoid papulosis, complete clinical history and laboratory findings are necessary to make the final and correct diagnosis. Although the pathogenetic relevance of the presence of CD30+ cells within the cutaneous infiltrate of patients with systemic TBC remains to be determined, our findings support the hypothesis that the TBC-associated cytokines' profile might not be strictly T<sub>H</sub>1-like, but a T<sub>H</sub>1-like to T<sub>H</sub>2-like switching may also occur.

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