JEADV (2003) **17**, 208–212

CASE REPORT

Specific immune therapy-related cutaneous B-cell pseudolymphoma with following dissemination

G Gerlini,† M Mori,† D Massi,‡ N Pimpinelli†*

*Departments of †Dermatological Sciences and ‡Human Pathology and Oncology, University of Florence Medical School, Florence, Italy. *Corresponding author, Department of Dermatological Sciences, University of Florence, Via degli Alfani, 37, Firenze, Italy, tel. +39 055 2344422; fax +39 055 2758757; E-mail: pimpi@unifi.it or nicopimpi@interfree.it*

ABSTRACT

We report two cases of cutaneous B-cell pseudolymphoma (PCBCL) induced by intradermal antigen injections for specific immune therapy (SIT). In both cases, the lesions had first developed on the area of injection; years later, new lesions appeared far from the original site. The histological, immunohistochemical, and molecular findings of the lesions showed features consistent with the diagnosis of PCBCL in both cases. In particular, the staining for sIg light chains showed a polyclonal pattern, and the molecular analysis by reverse transcriptase-polymerase chain reaction (RT-PCR) and Southern blot showed a germ-line configuration of the Ig heavy chain genes. While the development of PCBCL related to a specific stimulus is well known and widely reported, the development of histologically and immunohistologically identical lesions far from the injection site is definitely worthy of note. This behaviour might be due to the presence of retained antigens in the injection site. This chronic antigenic stimulation could induce the progressive selection – and subsequent dissemination – of antigen-specific B cell clones.

Key words: pseudolymphoma, B-cell, skin, specific immune therapy

Received: 23 January 2002, accepted 12 June 2002

Introduction

Cutaneous B-cell pseudolymphoma (PCBCL), otherwise known as cutaneous lymphoid hyperplasia (CLH), is a reactive B-cell hyperplasia that clinically and histologically mimics cutaneous B-cell lymphoma (CBCL).[1–4] Both primary cutaneous B-cell lymphoma (CBCL) and PCBCL share indolent clinical course and good response to non-aggressive treatment, therefore, these features are not crucial in the differential diagnosis. According to a widely accepted opinion, the only key diagnostic criteria to date are the demonstration of clonality (by immunohistochemistry and/or molecular analysis) and/or the correlation with known environmental stimuli: insect or arthropod bites, tattoos, infection by *Borrelia burgdorferi*.[5–10] In these latter conditions, skin lesions usually arise on the area affected by the specific trigger.

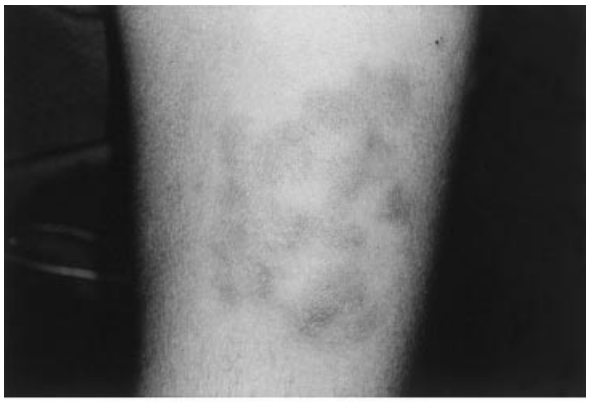
In this paper, we report two cases of PCBCL induced by subcutaneous antigen injections (specific immune therapy, SIT) in which, years later, the dissemination of lesions far from the injection site did occur.

Case reports

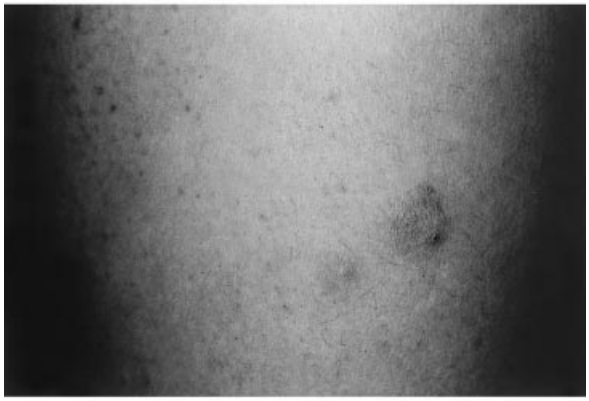
Case 1

A 30-year-old woman presented with erythemato-cyanotic plaques and nodules located on the lateral surface of both arms (fig. 1a), left buttock and left thigh (fig. 1b). The lesions of the arms had been present for 10 years, and developed soon after SIT by the coalescence of small papules and nodules. The patient had a family and personal history of atopy (rhinitis, atopic dermatitis). Total IgE and specific IgE for Parietaria and Graminaciae were increased, and prick tests for these latter allergens were positive. In addition, the patient was sensitized to nickel sulphate. The lesions on the left thigh and buttock had developed approximately 2 years before our observation.

A previous biopsy, taken from the right arm in another hospital, showed a dermal nodular lymphohystiocytic infiltrate with typical lymphoid follicles. A complete staging was carried out, including bone marrow biopsy, without any pathologic findings. New samples from both left arm and left thigh



a



b

fig. 1 (a) Patient 1. Erithematous and pigmented plaque on the lateral surface of left arm, site of previous (10 years) specific immune therapy. (b) Patient 1. Erythematous plaque of the left thigh. This and other skin lesions (left buttock) had developed approximately 8 years after that shown in fig. 1.

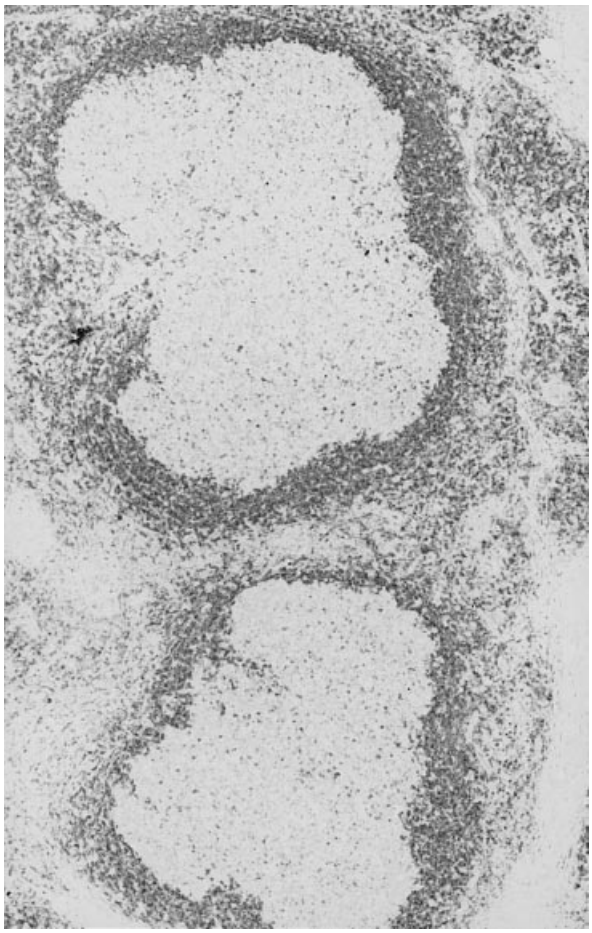


fig. 2 Patient 1, left thigh. Nodular and diffuse lymphohystiocytic infiltrate in the upper-mid reticular dermis, with presence of typical reactive lymphoid follicles (H&E, original magnification × 40).

lesions were taken and processed for routine histology, immunohistochemistry (fixed/embedded and frozen tissue), and molecular analysis. The histology showed the same pattern in both examined lesions: nodular and diffuse lymphohystiocytic infiltrate in the superficial and mid dermis, with presence of numerous typical reactive lymphoid follicles (figs 2,3). Immunohistochemical staining on paraffin sections showed that reactive follicles were mostly CD20+, although they occasionally harboured scattered CD3+ T-lymphocytes (fig. 4). The interfollicular areas were rich in T-lymphocytes (fig. 4), with isolated or small groups of B cells and CD68+ histiocytes. The reactive germinal centres were bcl-2 negative, contrasting with the positive cells in the mantles and interfollicular areas (fig. 5). The immunohistochemical analysis (APAAP technique) on frozen sections showed a mixed B- and T-cell infiltrate, with a distinct compartmentalization: nodular aggregates with typical features of secondary lymphoid follicles (CD22+ B cells with a CD5-/CD10+ phenotype associated with CD35+ follicular dendritic cells in the germinal centre; in the mantle, CD22+ B cells with CD5+/CD10- [mantle cell] or CD5-/CD10- [marginal cell] phenotype) were irregularly surrounded by 'interfollicular' areas in which CD3+, CD4+ T-cells and CD22+, CD5-, CD10- B cells were strictly intermingled. The staining for sIg light chains showed a polyclonal pattern (kappa/lambda ratio 4 : 1) in both areas. This finding was essential to establish the diagnosis of PCBCL. The molecular analysis by reverse transcriptase–polymerase chain reaction (RT-PCR) and Southern blot showed a germ-line configuration of the immunoglobulin heavy chain genes.

Case 2

A 47-year-old female presented in our Department with pigmented plaques on the lateral surface of both arms, thighs, buttocks and lower back. The lesions of the arms had developed, initially as grouped papules and small nodules, soon after SIT performed 18 years before. One year later, due to the persistence of such lesions, the patient was treated in another

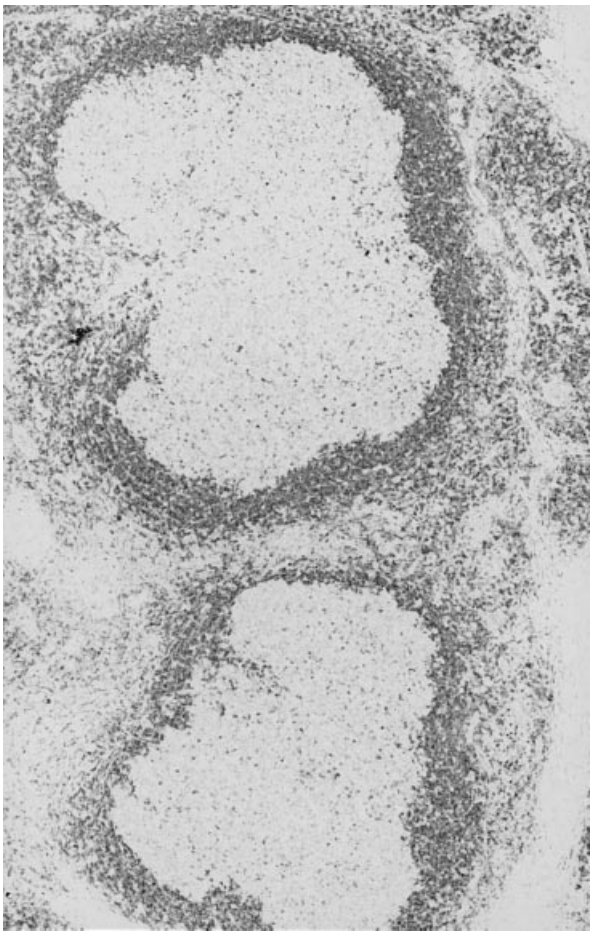


fig. 3 Reactive lymphoid follicles were composed of a central, pale staining germinal centre surrounded by a corona of small lymphocytes comprising the mantle zone (H&E, original magnification × 100).

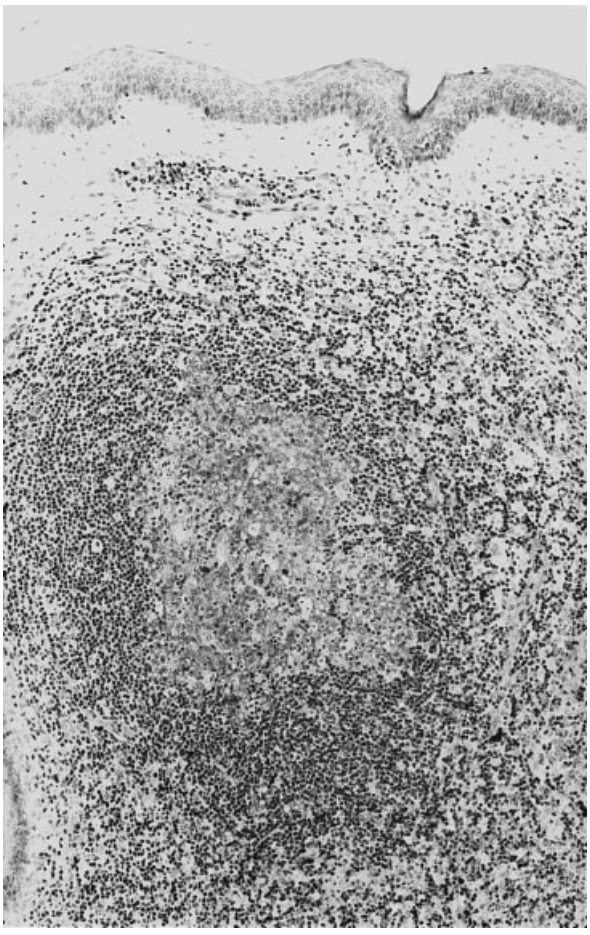


fig. 4 Immunohistochemical stain for CD3 shows that reactive lymphoid follicles occasionally harbour scattered CD3+ T-lymphocytes. These latter are clearly prevalent in interfollicular areas (APAAP, original magnification × 100).

centre by local radiotherapy with no improvement. To follow, she was treated by intralesional corticosteroids, with eventuation in thinner, pigmented plaques. The lesions on the thighs, buttocks and back had appeared about 2 years later as itching, pigmented and infiltrated plaques. The patient reported a 20-year-history of rhinitis and conjunctivitis induced by Graminaciae. Total IgE were highly increased (963 UI/mL), as well as specific IgE for Graminaciae. Prick tests were also positive.

A biopsy taken in another centre from lesions of the left arm showed a nodular and diffuse lymphohystiocitic infiltrate composed by T and B cells, these latter organized in typical lymphoid follicles with germinal centres in the mid and deep dermis. New biopsy specimens taken from both right arm and back were processed for histology, immunohistochemistry and molecular analysis. The histology showed the same pattern in both examined lesions: nodular lymphohystiocytic infiltrate in the superficial and mid dermis, with no evidence of histologically typical lymphoid follicles. The immunohistochemical analysis on frozen sections showed a single typical, secondary lymphoid follicle, irregularly surrounded by an infiltrate whose features were not different from those observed in the interfollicular areas in case 1. The staining for sIg light chains showed a polyclonal pattern (kappa/lambda ratio 3 : 1) in both follicular and perifollicular areas. The molecular analysis by RT-PCR and Southern blot showed a germ-line configuration of the immunoglobulin heavy chain genes.

Discussion

The interest of our cases essentially concerns the occurrence of new lesions far from the injection site of SIT some years after the development of primary lesions at the injection site. Indeed, cases of PCBCL resulting from antigen injections (pneumoallergens) for SIT and limited to the injection site have been previously reported.[11,12] In the cases reported herein, secondary lesions did not show any histological, immunohistological and molecular difference as compared to the primary ones.

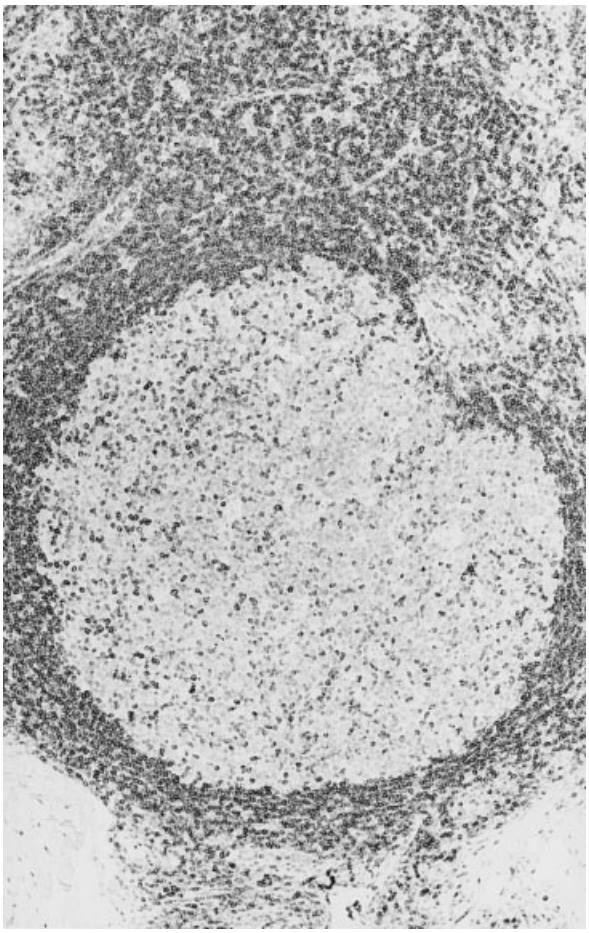


fig. 5 Immunohistochemical stain for Bcl-2 well distinguishes germinal centre cells from mantle zone B lymphocytes and adjacent T lymphocytes in the interfollicular areas, which strongly express this antigen (APAAP, original magnification × 200).

We might argue that SIT antigen(s) produce(s) a progressive selection of antigen-specific B cell clones, which subsequently spread from regional nodes to peripheral blood. These cells, which reasonably retain their skin-homing properties, can be recruited in the skin sites of contact with these airborne allergens. The above hypothesis, i.e. continuous antigenic stimulus producing selection and subsequent 'dissemination' of antigen-specific B cell clones, could explain the occurrence of disseminated B-cell pseudolymphoma.[13,14] Conversely, the cases reported here do not support the hypothesis, suggested and debated in the literature, of the progression of true PCBCL to CBCL.[6,15–17] In this regard, the development of CBCL related to *Borrelia burgdorferi* infection[9,10] is also particularly worthy of attention, due to close similarity between the concepts of *Helicobacter pylori* infection → acquired MALT (Mucosa-Associated Lymphoid Tissue)/MALT gastritis → MALT lymphoma on one hand, and of *Borrelia burgdorferi* infection → acquired SALT (Skin-Associated Lymphoid Tissue)/PCBCL → CBCL.[18–20] The hypothesis of a different sequential development of immune events related to SIT as compared to bacterial infections like those from *Borrelia burgdorferi* and *Helicobacter pylori*, with a lower likelihood to eventuate into (immune) dysplasia and neoplasia, can be reasonably suggested.

Speculations apart, it is a fact that we did not observe any histologic, immunohistologic and/or molecular signs of aberrancy in the lesions which had developed years after the primary ones far from the injection site, e.g. dendritic cells 'skipping' the germinal centre of reactive follicles, 'invasion' of reactive follicles by neoplastic cells of the interfollicular areas, or clonal rearrangement of Ig heavy chains.[5,6,15–17,19,20]

References

1 Burg G, Braun Falco O. *Cutaneous Lymphomas, Pseudolymphomas and Related Disorders*. Springer Verlag, Berlin, 1983.

2 Kerl H, Smolle J. Classification of cutaneous pseudolymphomas. *Curr Probl Dermatol* 1990; **19**: 167–175.

3 Rijlaarsdam JU, Willemze R. Cutaneous pseudolymphomas: classification and differential diagnosis. *Semin Dermatol* 1994; **13**: 187–196.

4 Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. *J Am Acad Dermatol* 1998; **38**: 877–895.

5 Santucci M, Pimpinelli N, Arganini L. Primary cutaneous B-cell lymphoma: a unique type of low-grade lymphoma – clinicopathologic and immunologic study of 83 cases. *Cancer* 1991; **67**: 2311–2326.

6 Rijlaarsdam JU, Bakels V, van Oostveen JW *et al.* Demonstration of clonal immunoglobulin gene rearrangements in cutaneous B-cell lymphomas and pseudo-B-cell lymphomas: differential diagnostic and pathogenetic aspects. *J Invest Dermatol* 1992; **99**: 749–755.

7 Pimpinelli N, Santucci M, Giannotti B. Cutaneous lymphoma: a clinically relevant classification. *Int J Dermatol* 1993; **32**: 695–700.

8 Willemze R, Kerl H, Sterry W *et al.* EORTC classification for cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment. *Blood* 1997; **90**: 354–371.

9 Garbe C, Stein H, Dienemann D, Orfanos CE. Borrelia burgdorferi-associated cutaneous B-cell lymphoma: clinical and immunohistological characterization of four cases. *J Am Acad Dermatol* 1994; **24**: 584–589.

10 Cerroni L, Zuchling N, Putz B, Kerl H. Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. *J Cutan Pathol* 1997; **24**: 457–461.

11 Bernstein H, Shupack J, Ackerman B. Cutaneous pseudolymphoma resulting from antigen injections. *Arch Dermatol* 1974; **110**: 756–757.

12 Lanzafame S, Micali G. Cutaneous lymphoid hyperplasia (pseudolymphoma) secondary to vaccination. *Pathologica* 1993; **85**: 555–561.

13 Torne R, Roura M, Umbert P. Generalized cutaneous B-cell pseudolymphoma. Report of a case studied by immunohistochemistry. *Am J Dermatopathol* 1989; **11**: 544–548.
14 Zackheim HS, LeBoit PE, Stein KM. Disseminated recurrent papular B-cell pseudolymphoma. *Int J Dermatol* 1997; **36**: 614–618.
15 Nakayama H, Mihara M, Shimao S. Malignant transformation of lymphoadenosis benigna cutis: a possibly transformed case and B-cell lymphoma. *Int J Dermatol* 1987; **14**: 266–269.
16 Wood GS, Ngan B, Tung R *et al.* Clonal rearrangement of immunoglobulin genes and progression to B cell lymphoma in cutaneous lymphoid hyperplasia. *Am J Pathol* 1989; **135**: 13–19.
17 Sangueza OP, Yadav S, White CR Jr *et al.* Evolution of B-cell lymphoma from pseudolymphoma. A multidisciplinary approach using histology, immunohistochemistry, and Southern blot analysis. *Am J Dermatopathol* 1992; **14**: 408–413.
18 Slater DN. MALT and SALT: the clue to cutaneous B-cell lymphoproliferative disease. *Br J Dermatol* 1994; **131**: 557–561.
19 Giannotti B, Santucci M. Skin-associated lymphoid tissue (SALT)-related B-cell lymphoma (primary cutaneous B-cell lymphoma). *Arch Dermatol* 1993; **129**: 353–355.
20 Pimpinelli N, Santucci M. The skin-associated lymphoid tissue-related B-cell lymphomas. *Sem Cutan Med Surg* 2000; **19**: 124–129.