The many faces of lymphomatoid papulosis

John R Goodlad

Abstract

Lymphomatoid papulosis was first described in 1968, but the pathological spectrum associated with this diagnosis continues to expand. Initially two main morphological subtypes, types A and B, were proposed, followed shortly by a type C. However, in the past few years, several additional variants have been described, a putative type F being the current position reached in the alphabet. Clinically, all the morphological subtypes behave in a similar indolent fashion with spontaneous resolution of lesions. Conversely, many of the disease entities that enter the pathological differential diagnosis are malignant and often highly aggressive neoplasms. These include mycosis fungoides, transformed mycosis fungoides, pagetoid reticulosis, primary cutaneous CD8-positive aggressive epidermotropic T-cell lymphoma, primary cutaneous γ/δ T-cell lymphoma and extranodal NK/T-cell lymphoma, nasal type. For certain subtypes of lymphomatoid papulosis, distinction from aggressive lymphoma is not always possible on pathological grounds and clinicopathological correlation remains essential in arriving at the correct diagnosis.

Keywords cutaneous; differential diagnosis; lymphoma; lymphomatoid papulosis; pathology; skin

Introduction

The term lymphomatoid papulosis was first used in 1968 by Warren Macaulay to describe a continually self-healing eruption that was clinically benign but histologically malignant, that he had encountered in one of his patients, and which he likened to other sporadic reports of similar sounding cases reported elsewhere under a variety of different names.[1] The terminology persists to this day and the clinical descriptions of this entity have remained largely unchanged over succeeding years. Conversely, an ever-increasing variety of pathologies have been described in association with the typical clinical picture, an awareness of which is essential in arriving at a correct diagnosis and ensuring appropriate patient management.

Clinical features

Most patients are adults, although LyP may also be encountered in the paediatric age group.[2] Patients present with crops of erythematous papules that develop over 3–4 weeks, undergo necrosis and ulceration, then heal spontaneously. Complete resolution usually takes 3–12 weeks and may leave persisting atrophic scars.[2] There can be anything from a few, up to hundreds of lesions. Trunk and limbs are most frequently affected but more acral sites can also be involved, as can the oral cavity. In children, the clinical picture is sometimes complicated by the presence of large rapidly developing ulcerating nodules alongside more typical papular lesions, but spontaneous regression is still the rule. Although lesions tend to be grouped, they are often in different stages of evolution at any one time. The overall course may be relatively short, lasting only a few months, or more chronic with recurrent bouts of disease occurring over 10 years or more.

Treatment is rarely required, and usually only considered for cosmetic reasons and/or if lesions are particularly numerous. In such instances either phototherapy (PUVA) or low dose methotrexate have proven most effective in rapidly achieving complete remission, although sustained remission is rarely achieved. Multiagent chemotherapy is to be avoided. Although its use results in reduction or clearance of lesions, rapid recurrence is the norm after treatment cessation or even during treatment. This ineffectiveness is compounded by the inherent side effects and long term complications of such toxic therapy.[3]

Pathological features

When a patient presenting with clinically typical LyP is biopsied, a variety of pathologies may be encountered. An awareness of this spectrum of appearances is essential, since several of the histological and/or phenotypic patterns can easily be mistaken for much more aggressive lymphomas raising the potential for gross overtreatment of the patient with potentially toxic therapies. Historically, and contemporaneously, the different pathological patterns of LyP have been subdivided into subtypes or variants, each designated by a letter of the alphabet. This subdivision is rather arbitrary, not least because there is a considerable degree of overlap between many of these subgroups, and since more than one subtype may be present at different sites, in the same tissue or at different times in a single patient. Nevertheless, the proposed subtypes are useful in illustrating the pathological spectrum of changes for which a diagnosis of LyP should be considered, particularly when clinical information is lacking. What follows are the major pathological patterns encountered in LyP, with reference made to the putative subtype to which they correspond.

Lesions characterized by large CD30-positive anaplastic T-cells; LyP types A & C

The prototypic neoplastic cells in LyP are large CD30-positive anaplastic blasts of T-lineage (Figure 1). These possess abundant cytoplasm, pleomorphic vesicular nuclei and prominent nucleoli. In some cells the nuclei may be bilobed or multilobated.

Morphology: in the majority of cases (approximately 80%) of LyP, the CD30-positive cells are scattered individually or are arranged in small clusters within a polymorphic infiltrate rich in small lymphocytes, histiocytes, plasma cells, neutrophils and eosinophils (Figure 2). The infiltrate is typically perivascular and although centered within the reticular dermis , there is usually involvement of the papillary dermis and sometimes the subcutaneous fat. A wedge-shaped configuration of the infiltrate is often described, the base of the wedge lying in close apposition to the epidermis. This pattern of LyP is usually referred to as type A.[4]

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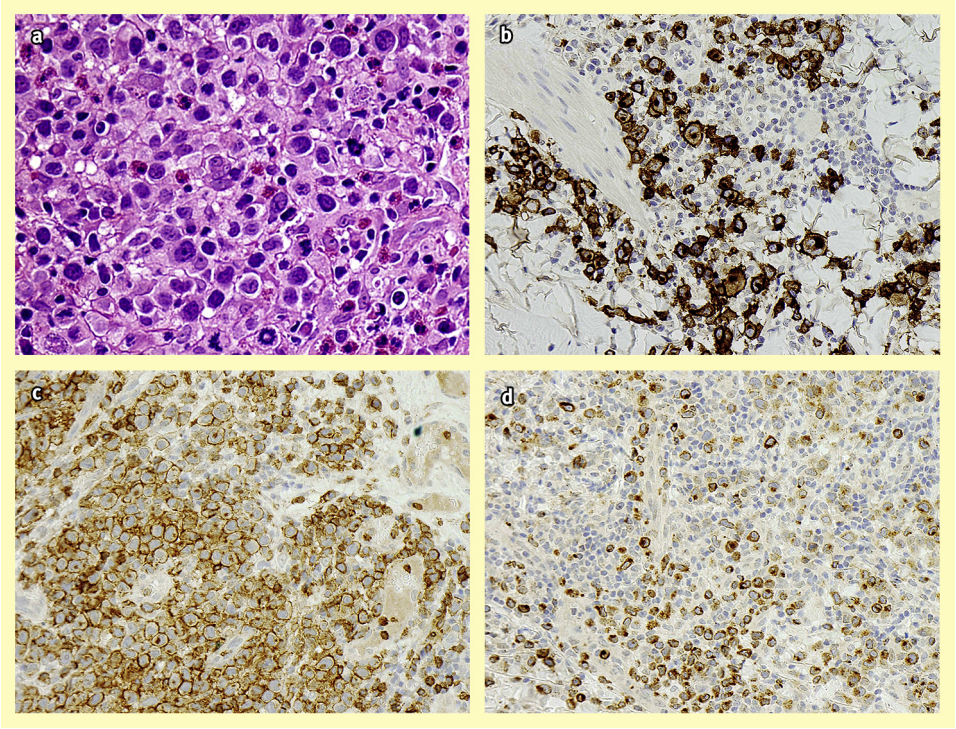

Figure 1 The characteristic cell in lymphomatoid papulosis types A and C is a large anaplastic blast cell with abundant cytoplasm, vesicular nucleus and prominent nucleolus (**a**). Typically there is expression of CD30 (**b**), CD4 (**c**) and at least one cytotoxic molecule, such as perforin (**d**).

In type C LyP there are relatively few background inflammatory cells and the CD30-positive anaplastic large cells form large clusters or cohesive sheets, or account for >50% of the total infiltrate (Figure 3). The appearances are identical to primary cutaneous anaplastic large cell lymphoma and distinction is only possible on clinical grounds (see below).[4]

Epidermotropism is encountered relatively frequently in both patterns and central ulceration can be present. In addition, epidermal hyperplasia can be seen, and in some cases this is striking with features amounting to pseudoepitheliomatous hyperplasia.[4]

Phenotype: the large atypical cells in type A and type C show the same phenotypic characteristics. They are characterized by strong expression of CD30 and also typically express CD4. Despite being negative for CD8 they are usually positive for one or more of the cytotoxic molecules TIA-1, granzyme B and perforin (Figure 1).[2] There is variable but frequent loss of pan-T-cell antigens such as CD2, CD3 CD5 and CD7, although 'null cell' phenotypes are uncommon. Staining for CD45 is usually positive but the cells are negative for CD15, EMA and ALK1.[5]

In a proportion of patients the phenotype deviates from the above. Expression of CD8 rather than CD4 is occasionally seen, although one group reported a slight predominance of CD8-positive type A cases in adults and a marked excess of CD8-positive LyP type A cases in the paediatric age group.[6,7] Rare cases of CD56-positive LyP have also been documented.[8]

Lesions with prominent epidermotropism: LyP types B & D

As mentioned above, a degree of epidermotropism is not unusual in LyP types A and C. However, a subset of cases is characterized by pronounced epidermotropism and a predominance of smaller T-cells with cerebriform nuclei, the overall picture bearing a strong resemblance to mycosis fungoides. Such cases were originally categorized as type B LyP, but more recently another epidermotropic variant has been described and assigned the letter 'D' for its subtype.

Morphology: in type B LyP there is a dominant epidermotropic infiltrate of small to medium size lymphocytes with cerebriform nuclei that colonize the basal and parabasal layers of the epidermis. Few, if any, large atypical blast cells are seen.[4] There is also usually a band-like or perivascular infiltrate of similar cells in the papillary dermis. Small lymphocytes may also be present, as may neutrophils and eosinophils, but not always, and only in small numbers.

Marked epidermotropism is also a feature of LyP type D and is associated with prominent epidermal hyperplasia, giving rise to a pagetoid reticulosis-like appearance (Figure 4). The infiltrate is composed of slightly larger cells than seen in type B lesions, these being of medium size with pleomorphic nuclei. Similar cells also form a dermal infiltrate in most cases and this may extend into the reticular dermis and even subcutaneous fat.[9] Large anaplastic cells, as seen in LyP types A and C are rare or absent, and neutrophils and eosinophils are typically not seen.[9]

Phenotype: the phenotype of LyP type B has not been as extensively investigated or reported as in Lyp types A and C. The intraepidermal lymphocytes are typically CD3 and CD4-positive, and negative for CD8.[2,10] The main classification systems state that staining for CD30 is negative,[2,10] but some authors appear to accept the presence of at least some CD30-positive cells within