CASE REPORT

An uncommon diagnosis for a recurrent erythematous patch in a paediatric patient

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SUMMARY

A 14-year-old girl presented with a circular erythematous patch over the left buttock for approximately 10 years, with ongoing ulceration and papules developing over the last 4 years. Punch biopsies were taken within and above the patch for diagnosis. Both revealed marked inflammatory infiltrates with atypical, irregular lymphocytes and increased mitosis. Immunostaining revealed CD8 positivity and a pan T helper cell phenotype. T cell receptor gene rearrangement analysis showed T cell clonality in both biopsies. These findings were consistent with mycosis fungoides and associated lymphomatoid papulosis. Both are rare conditions but have been associated in 5%–20% of cases. A definitive association has not yet been established; however, T cell monoclonality shows 50%–60% share a common origin. Management options are extensive with no one treatment showing superiority. Our patient received low-dose radiotherapy with good outcomes, but subsequently required further radiotherapy.

BACKGROUND

This case is unusual as both mycosis fungoides (MF) and lymphomatoid papulosis (LyP) are rare conditions, and although they have shown documented associations, this does not occur in all cases.^{1–3} Additionally, our case showed a CD8 majority, whereas classically, MF often demonstrates CD2, CD3, CD4 and CD5 positivity. Although, some studies have previously documented that paediatric populations can show a predominantly CD8 majority.

Furthermore, LyP is more commonly seen in elderly populations favouring a slight male preponderance, whereas our case was a paediatric female patient.^{2–5} However, LyP has also been documented in younger individuals; but patients can be older at presentation due to delays in diagnosis given their largely indolent progression. Importantly, this patient was initially treated as eczema for many years; highlighting the significance of re-evaluating an alternative diagnoses, as this may be more probable if a condition remains refractory to appropriate treatment.

Lastly, although both typically favour indolent courses, LyP can be associated with malignancy, and MF can have significant consequences. Therefore, clinicians must have a high index of suspicion for these conditions, to adequately recognise and refer to specialists for ongoing management.

CASE PRESENTATION

A 14-year-old girl presented with a 10-year history of an erythematous circular patch over the left buttock. Within the last 4 years, recurrent erythematous papules with necrosis and ulceration developed. She was asymptomatic, systemically well and had no significant medical, drug or allergy history. On examination, a 10×15 cm circular erythematous patch with silvery papules and keratin plugs was seen (figure 1). Initially, the patch had been treated as eczema, and although emollients and topical steroids had helped, the lesions persisted. Over time, the patch enlarged with prominent erythema and ulcers requiring recurrent antibiotic therapy, prompting a dermatology referral.

INVESTIGATIONS

Two 3 mm punch biopsies were taken from within and above the patch. Both biopsies contained marked inflammatory infiltrates.

The patch biopsy depicted irregular chronic inflammation in the upper dermis with lichenoid features and a disrupted epidermal base (figure 2). There was mild spongiosis, parakeratosis, epidermal acanthosis with hyperkeratosis and slight elongation of the rete ridges. Additionally, lymphocytic exocytosis, cytological atypia and large, irregular intraepidermal lymphocytes were seen. The dermis showed moderate mononuclear cell infiltration with lymphocytes, histiocytes and atypical cells. Immunostaining revealed: CD2, CD3, CD4 and CD8 positivity, with a CD8 majority.

Figure 1 Erythematous circular patch on the left buttock measuring approximately 10×15 cm.

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Figure 2 Histology of the patch with inflammatory infiltrates and large atypical cells (H&E stain, magnification $\times 40$).

The second biopsy revealed complete epidermal ulceration, necrosis with fibrin and inflammatory debris containing bacterial colonisation. The dermis showed a mixed inflammatory infiltrate, with lymphocytes, exocytic neutrophils, histiocytes and prominent eosinophils. There were large cells with pale cytoplasm, hyperchromatic and atypical irregular nuclei with increased mitotic activity (figure 3). Immunostaining showed: CD30 (figure 4), CD2, CD3, CD4, CD5 and CD45 positive large cells, depicting a pan T helper cell phenotype. The biopsy was negative for endomysial antibody, activin receptor-like kinase 1 and CD56.

T cell receptor gene rearrangement analysis (TCRGRA) was performed on both biopsies. This showed a shared clonal T cell population from both biopsies when peak sizes were compared. This demonstrated immunophenotypically different populations of CD8 positive MF cells with concomitant CD4 positive LyP cells originating from a clonally related population.

Figure 3 Histology above the patch showing mixed inflammatory infiltrates with increased mitosis (arrows depicting cells with increased mitotic activity) (H&E stain, magnification $\times 40$).

DIFFERENTIAL DIAGNOSIS

On presentation to dermatology, differential diagnoses included MF or naevoid psoriasis. However, the differentials must be kept broad as MF can appear similar to many different clinical and histological diagnoses described below.

Linear naevoid psoriasis (LNP) is an atypical presentation of psoriasis, forming along the lines of Blaschko secondary to migration of somatically mutated cells during embryogenesis.⁶ Some authors dispute its existence and feel it represents a spectrum of inflammatory linear verrucous epidermal naevus (ILVEN). However, cases with both conditions have been previously observed. Classically, LNP presents in later life, with rapid progression and involves sites associated with psoriasis, for example, nails and scalp. Often, a family history exists, and the condition responds well with topical antipsoriatic treatment. Comparatively, ILVEN occurs in early life with pruritus, no nail or scalp involvement, and although classically progresses over years, it is often refractory to therapy.

MF has multiple differentials and is difficult to diagnose initially given its indolent progression.^{7,8} It is a primary cutaneous T cell lymphoma (CTCL) formed by malignant transformation of CD4 +ve T cells in the skin but can progress to involve the lymphatic system or organs.^{7,8} It remains the most common CTCL, occurring largely in adults but can affect paediatric populations. Some studies estimate 0.36 cases/100 000 patients per year; however, this figure is likely to be higher given the increasing number of malignancies and misclassification of MF as other CTCLs. The exact aetiology of MF remains unclear, and clinical presentation varies depending on its stage and duration. It generally, although not exclusively, evolves through three stages of patch, plaque-stage and tumour-stage disease, although erythroderma can also rarely present.^{7,9} Commonly photoprotected areas such as the buttocks and groin, thighs, axilla and submammary regions are affected, although organs and mucosa can be involved.⁶ MF generally has an indolent course, with many never progressing to tumour-stage disease; thus, the prognosis is generally favourable. During tumour-stage disease, large cells and increased atypical lymphocytic mitosis can be seen with occasional CD30 positivity. However, diagnosis of MF at any stage can take on average 3–6 years and given the malignant potential, correct diagnosis and follow-up is essential as survival diminishes with advancing disease.^{7,8} Typically, if MF proves fatal, it is due to systemic involvement or severe infections.

Other differentials that closely resemble MF particularly in the early stages include: eczema psoriasis, lupus, inflamed vitiligo, spongiotic dermatitis, infections/infestations such as tinea, scabies and syphilis, lymphomatoid drug reactions, lymphomatoid contact dermatitis and chronic actinic dermatitis (CAD).^{7,8} Early stage MF is challenging, as it often lacks atypical lymphocytes, has non-specific changes consistent with other dermatoses and has multiple histological subtypes. However, subtle epidermotropism can sometimes help distinguish MF from other inflammatory conditions. T cell cloning and immunostaining can be of benefit but are less likely to be diagnostic in early stage MF. Plaque-stage MF is easier to diagnose than patch-stage disease given the denser infiltrate and increased epidermotropism. In cases with inconclusive diagnosis, multiple biopsies are advised to avoid misdiagnosis.

Clinically, eczema should respond favourably with topical emollients and steroids. Therefore, in this case, lack of response to topical steroids should prompt consideration of either systemic therapy if eczema is the definitive diagnosis or biopsies for consideration of an alternative diagnosis.⁷ Psoriasis generally

Figure 4 Histology above the patch depicting CD30 positivity (CD30 cells demonstrated by arrows and staining) (CD30 immunostaining, magnification $\times 20$).

has erythematous plaques in an extensor distribution but can predicate within the groin region similar to MF. However, psoriasis histologically demonstrates dilated dermal vessels, parakeratosis with neutrophils and decreased epidermotropism.

In allergic or drug-induced dermatoses, these should resolve naturally over time once identification and removal of the offending agent has occurred.⁷ In challenging cases, if suspicion remains high, patch testing can be performed against the suspected agents.⁸

CAD occurs largely in men in photoexposed areas and can result in erythroderma.^{7,8} This is a different clinical pattern to classical MF, therefore, can be differentiated via good history taking. Alternatively, phototesting with ultraviolet A or ultraviolet B light can also confirm CAD.

Histologically, nodular scabies can mimic MF via dense lymphocytic infiltrate with eosinophils, occasional T cell and Pautrier-like microabscesses.⁸ Identification of the mites is crucial in confirming the diagnosis. Tinea and candidiasis are infections that also demonstrate a band-like lymphocytic infiltrate and exocytosis similar to MF, but can be excluded via periodic acid–Schiff staining.

Lastly, T cell pseudolymphomas (which can also be secondary to recurrent arthropod bite reactions) can mimic MF.⁸ Clinical presentation involves lymphadenopathy, hepatosplenomegaly, arthralgia, fever and erythematous eruption, usually secondary to medications especially antiepileptics. Histologically, band-like infiltration, dermal cerebriform nuclei and epidermal Pautrier-like microabscesses can be seen which can appear similar to lymphomatoid dermatitis, allergic contact dermatitis and MF. However, careful history taking and withdrawal of any offending agent will result in resolution of lesions other than MF.

Overall, a good knowledge of clinical features and presentation of diseases is essential. Where diagnostic uncertainty remains, repeat biopsies should be considered with utilisation of experienced histopathologists.

TREATMENT

Our patient was given low-dose superficial radiotherapy via 8 Gy in two fractions with initially good outcomes. She subsequently

required further radiotherapy and is having ongoing specialist follow-up with dermatology.

OUTCOME AND FOLLOW-UP

She remains systemically well with ongoing dermatology follow-up and low-dose radiotherapy.

DISCUSSION

LyP and MF are both rare conditions but have been associated in 5%–20% of cases.^{1,2} It is unclear whether they develop independently or one precedes the other.^{1–3} Some studies suggest a common clonal origin, but no exact link has been conclusively proven.^{2,3} Using T cell monoclonality, only 50%–60% of LyP lesions and MF show common origin; this decreases during early-stage MF. Combinations of LyP and MF appear to demonstrate favourable prognosis, particularly with early MF (stage IA or IB).

MF is rare, but remains the most prevalent CTCL, favouring older and male populations.¹ Clinically, erythematous plaques, patches or nodules are possible, with indolent progression. Prognosis varies according to size, location and extracutaneous spread. The median survival of stage IA is 33 years versus 11 years for stage IB or IIA. Erythroderma, extracutaneous disease or large-cell transformation has higher mortalities, but remains uncommon. MF varies histologically but can contain small cells with cerebriform nuclei, few large cells and band-like lymphocytic infiltration, with CD2, CD3, CD4, CD5 and rarely CD8 positivity. Although paediatric populations can demonstrate CD8 positivity. TCRGRA will show some clonality, but this is harder to detect in the earlier stages.

LyP is a CD30 positive primary cutaneous lymphoproliferative disorder, considered histologically malignant but clinically benign.^{4,5} It can occur at any age but typically affects patients in their 50s. Although LyP is a benign condition, malignancies have been associated in approximately 10%–20% of cases. However, it remains unclear why malignancies arise in some and not others. Furthermore, LyP can present at any stage pre-tumour/post-tumour development, this creates further confusion if LyP is simply coincidental or contributes to the likelihood of malignancy. Malignancies associated with LyP include MF, primary cutaneous anaplastic large-cell lymphomas (pcALCL) and Hodgkin's lymphoma. Largely, lymphomas are observed; however, other non-lymphomatoid tumours have transpired. Clinically, recurrent pink-purple erythematous papulonodular eruptions, crusting or vesicles with spontaneous involution are observed.^{4,5} Small or very large lesions are more likely to involute, and generally, observation alone is required.

Histologically, LyP has three main subtypes (A–C), although six in total have been documented (A–F). Type A has large atypical lymphocytes resembling Reed–Sternberg cells. They are CD30 +ve with a slight CD4 versus CD8 predominance; occurring in younger populations (mean age of 45 years). Type A CD30 cells can be found in small clusters or in isolation, forming wedge shapes with perivascular infiltration of polymorphs close to the epidermis.¹⁰ Both types A and C predominately express CD4; however, CD8 expression has predominated in some studies of paediatric populations,^{5,11} and CD56 has also rarely been reported.

Type C has fewer background inflammatory cells, large anaplastic CD30 +ve cells forming sheets or clusters, appearing similar to pcALCL.¹⁰ This also occurs in younger populations (average age of 45 years) and tends to resolve spontaneously. Types A and C are the most commonly documented subtypes in most studies.

Type B has smaller T cells with cerebriform nuclei in the basal/parabasal layers, a band-like perivascular infiltrate and epidermotropism appearing similarly to MF.^{10 12} Cells are usually positive for CD3 and CD4 and rarely for CD56 or CD8 and variable expression for CD30, occurring in older populations (average age of 60 years).

Similarly, type D has epidermotropism with prominent epidermal hyperplasia but contains larger infiltrates than type B.^{10 12} Conversely, type D has CD8 positive cells expressing CD30 and cytotoxic molecules with negative CD4 and CD5. However, there can often be misclassification between B and D, with cell size being the main differentiating factor.

Type E shows fewer papules/nodules but larger ulceration and crusting, persisting for 3–6 weeks before resolving spontaneously.^{10 12} Histologically, there is angiocentric infiltration of pleomorphic lymphoid cells (largely eosinophils and neutrophils) which destroy small to medium blood vessels. Additionally, epidermal and dermal necrosis with dermal oedema can occur, plus folliculotropism or epidermotropism with lymphocytic 'rimming' of subcutaneous adipose cells. The invading lymphocytes show CD8, CD30, CD2 and CD5 positivity but have variable expression for CD3 and CD7.

Type F is characterised by increased folliculotropism, but this could be true of any of the subtypes of LyP, thus Type F may not truly be a new subtype.¹⁰ However, it is difficult to subtype LyP given its histological complexity; thus, clinical and histological correlations are needed for diagnosis.

Patients usually express one subtype, but multiple subtypes can occur which increase the malignancy potential.⁵ The association of LyP with malignancy remains unclear; however, studies have considered age, gender, infections, disease severity and chemokine receptors.⁴ Only gender showed significance with men demonstrating 2.5× higher risk of developing lymphoma. Majority of men with lymphoma tend to have pcALCL, and women favour MF. Some papers suggest increased risk of lymphoma progression with a positive TCRGR and a mixed

subtype. However, the average time for tumour development is 17.6 years, thus, follow-up and aetiology can be challenging to establish.^{4 5} Lastly, patients with LyP often have other concurrent malignancies, for example, haematological, prostate, colon, breast, uterine, lung, thymoma, melanoma and medulloepithelioma. Treatment with phototherapy, topical corticosteroids, antibiotics or methotrexate has historically made little difference to patients with LyP.

Management options for MF with LyP include observation, phototherapy, corticosteroids, low-dose methotrexate or superficial low-dose radiotherapy.^{1–5} Some studies observed that these treatments did not significantly affect the disease course on a 4-year follow-up. Our patient had low-dose superficial radiotherapy (8 Gy in two fractions) with good outcome. She subsequently required further radiotherapy.

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Learning points

- Mycosis fungoides (MF) with associated lymphomatoid papulosis (LyP) is a rare but an important diagnosis to consider in lesions refractory to common topicals.
- Biopsy or multiple biopsies should be considered for challenging diagnoses, and expert histopathological assessment should be sought, particularly given the varied histological presentations of MF.
- Management can be frustrating as MF and LyP respond poorly to therapy, and although largely indolent patients can be concerned given the potential risks of malignant progression.

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