infection, prompting a test for EBER ISH. EBER was positive in more than 75% of the neoplastic lymphocytes in follicular pattern with co-expression of BCL2, BCL6, CD10 and CD20, fulfilling the criteria of EBV-positive follicular lymphoma. However, unlike other cases,^{2,4,8} our case did not transform to EBV-positive high-grade lymphoma, but rather to EBV-negative high-grade lymphoma. Interestingly, we found that the percentage of EBV-positive neoplastic cells showed dynamic change at different time points and at different anatomical sites. EBER was positive early, but in only a minority of neoplastic cells. The population and proportion of EBV-positive neoplastic cells expanded with time, up to more than 75% of lymphoma cells in the lymph node. At the same time, EBV-positive neoplastic cells accounted for only 5% of the lymphoma cells in bone marrow. Micro-environment factors, chemotherapy and/or immune dysregulation might play a role in selecting EBV-positive cells. Nevertheless, based on the chronological change in this case, we found that *BCL2* was rearranged early in the follicular lymphoma, and then EBV infected some lymphoma cells with clonal expansion, particularly in the lymph node, forming EBV-positive follicular lymphoma. Because EBV was positive early in the previous follicular lymphoma 7 years ago, clonal B-cell expansion driven by EBV reactivation was suggested. However, the EBV-negative lymphoma cells underwent high-grade transformation and clonal expansion after acquiring *MYC* rearrangement later, in addition to the underlying *BCL2* rearrangement, that led to the transformation to EBV-negative double-hit lymphoma and mortality of this patient.

In addition to this case, we also performed EBER *in situ* hybridisation in 54 cases of follicular lymphoma in our archives (from 2012 to 2021), including 42 cases of WHO grade 1–2, 10 cases of grade 3A, and two cases of grade 3B. Of these, 14 cases were associated with DLBCL, while none were associated with double-hit lymphoma. All 54 follicular lymphomas were EBV-negative. Interestingly, one EBV-positive DLBCL case was associated with EBV-negative follicular lymphoma, WHO grade 1–2. The prevalence of EBV-positive follicular lymphoma, WHO grade 1–2, was 2.3% (1/43) in our data. Although our sample size was relatively small, we used the full tissue sections in order to avoid missing cases with partial EBER positivity. Nevertheless, the prognosis of EBV-positive versus EBV-negative low-grade follicular lymphoma is still unclear.

In summary, we present an extremely rare case of EBV-positive low-grade follicular lymphoma transforming to EBV-negative double-hit lymphoma. Despite most reported cases of EBV-positive follicular lymphoma not demonstrating specific morphological features to predict EBV positivity, our case showed geographic necrosis with nuclear debris and vague granuloma, which was unusual for conventional follicular lymphoma, suggesting possible EBV infection. We propose that apart from screening for EBER in high-grade follicular lymphoma, low-grade follicular lymphoma showing geographic necrosis with nuclear debris, vague granuloma, HRS-like cells and/or angioinvasion should also be tested for EBER to select EBV-positive low-grade follicular lymphoma, which tends to transform to higher-grade lymphoma with worse prognosis.

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Cutaneous lymphoplasmacytic lymphoma with *MYD88* L265P mutation, bone marrow involvement, and paraproteinaemia

To the Editor,

We present four cases of cutaneous small B-cell infiltrates classified as cutaneous involvement by lymphoplasmacytic lymphoma (LPL). Three patients had a known history of *MYD88* mutated LPL and presented with cutaneous recurrences, and one patient presented with a primary cutaneous lesion. The clinical presentation included three cases with single erythematous skin nodules on the trunk, the upper extremity (Fig. 1A), and ear (Fig. 1B), and a diffuse papular and macular rash on the trunk in one case (Fig. 1C,D). Polymerase chain reaction (PCR) for *MYD88* L265P mutation was positive in the

Fig. 1 Clinical macroscopic photographs of (A) upper extremity nodule of Case 1, (B) skin lesion of the right ear of Case 3, and (C) macular and papular skin rash of Case 4 involving the whole torso, with (D) a close-up of the erythematous macules and papules. (E) Histological section demonstrating the skin punch biopsy findings of the macular and papular rash of Case 1 (H&E). (F) Two histological sections demonstrating the alternative perivascular and nodular superficial and dermal infiltrates in the shave biopsy of the skin nodule in Case 1 (H&E).

Fig. 2 (A) Immunohistochemistry (IHC) for CD21 performed on skin punch biopsy of macular and papular rash in Case 1 (Fig. 1E) shows lack of follicular dendritic meshworks. (B) IHC for kappa (left) and lambda (right) immunoglobulin light chains performed on the skin punch biopsy of the macular and papular rash in Case 1 (Fig. 1E). (C) Bone marrow biopsy findings in Case 1 with bone marrow involvement by lymphoplasmacytic lymphoma. (D) Bone marrow aspirate examination in Case 1 demonstrated prominent lymphoplasmacytic lymphocytes and increased plasma cells (oil immersion, 100×). (E) Cytogenetic assessment with karyotyping of the bone marrow revealed loss of a long arm of chromosome 6 (monosomy 6q) and a gain of the short arm (trisomy 6p).

skin biopsies from all patients. All patients had lymphadenopathy, none showed splenomegaly, and the concurrent bone marrow specimens showed involvement of the bone marrow by plasmacytoid B-cells, representing up to 70% of total cellularity in all cases. Serum electrophoresis was positive for an IgM and IgG paraprotein in three and one patient(s), respectively. No patient was treated with local radiation and the clinical course was marked by progression in three of four cases. The clinicopathological findings are summarised in Table 1.

Histopathologically, lymphoplasmacytic differentiation was present in all cases, as was immunoglobulin light chain restriction of the same isotype as the monoclonal serum paraprotein. Cutaneous manifestations of LPL have been rarely described as nodular and erythematous plaques and patches, as was seen in three of our cases.¹ A diffuse rash arising on the chest was seen in two of our cases. The histopathological findings showed a Grenz zone separating an attenuated epidermis from a dense, diffuse dermal lymphoplasmacytic infiltrate without lymphoid follicle formation in some cases (Fig. 1E). Others demonstrated an unremarkable epidermis with a perivascular lymphoplasmacytic infiltrate without eosinophils. The morphological distribution appears to exist on a spectrum, as Case 1 presented as superficial perivascular and deep dermal infiltrates in the same biopsy (Fig. 1F). Importantly, besides both histopathological patterns within the same biopsy of a nodular lesion, we document the occurrence of both rash-like and nodular patterns of cutaneous eruptions at different time points in the same patient (Case 1).

Primary cutaneous follicle centre B-cell lymphoma (pcFCL) and primary cutaneous extranodal marginal zone lymphoma (pcMZL) are the main neoplastic differential diagnostic considerations of cutaneous LPL.² Besides the prominent lymphoplasmacytic differentiation expected in LPL, variable staining with plasma cell markers and the absence of germinal centres and follicular dendritic cell meshworks (Fig. 2A) are important clues arguing against pcFCL and pcMZL.

Although the former may rarely display similar features,³ distinction from the latter may be even more challenging on histopathological and immunophenotypical grounds. A constant feature in all of our reported cases was the strong expression of monotypic immunoglobulin light chains (Fig. 2B). This finding would not be expected to be uniformly

present in all cases of pcMZL. Presence of the *MYD88* mutation rules out pcFCL,³ but the presence of *MYD88* mutation alone may not be completely diagnostic, as some cases of pcMZL purportedly harbour the mutation. A report from Wobser *et al.* described *MYD88* mutations in up to 6% of pcMZL (3/51 cases), and all three cases with *MYD88* mutations in their series belonged to the IgM positive subtype.⁴ Importantly, in two of three patients from the Wobser *et al.* series, *MYD88* mutations other than that leading to the protein change L265P were identified. Conversely, all four patients in our series showed this specific protein change. In their case series, Carlsen *et al.*⁵ showed that none of six non-class switched IgM positive pcMZLs showed *MYD88* mutations.

Finally, in a series including 45 cases of pcMZL, Brenner *et al.* reported that all cases exhibited *MYD88* wild-type.⁶ Current literature further asserts that pcMZLs preferentially express IgG, IgA, or IgE, and stand in contrast to non-cutaneous marginal zone lymphomas, which preferentially express IgM.^{7–10} The morphological and immunophenotypical overlap between cutaneous involvement by LPL and pcMZL make this distinction challenging, and it is unclear whether pcMZL with *MYD88* L265P mutations actually exist, or whether these cases represent cutaneous manifestation of an underlying LPL with undetected IgM paraproteinaemia, lymphadenopathy, and bone marrow involvement.

Both pcFCL and pcMZL are known for their clinically indolent behaviour, and are usually treated with local radiation therapy and have excellent 5-year progression-free survival.¹¹ In contrast to the usual course of pcMZL, three of our cases showed progression under therapy. Features that may be helpful in excluding a cutaneous presentation of LPL include: an appropriate clinical history (cryoglobulinaemia, neuropathy, cold agglutinin disease, lymphadenopathy), as well as serum protein electrophoresis (SPEP) testing. Even in the absence of systemic symptoms, we recommend SPEP prior to a new diagnosis of pcMZL, especially if prominent reactive lymphoid follicles characteristic of pcMZL are missing, and/or if the plasmacytoid component with brisk immunoglobulin light chain restriction predominates in the lesion. PCR for detection of the *MYD88* L265P mutation works well in formalin-fixed and paraffin-embedded tissue sections from skin biopsies, and should be pursued for cases in which SPEP is unattainable or

Table 1 Clinicopathological findings

	Case 1	Case 2	Case 3	Case 4
Age, sex	73, M	76, M	66, F	71, M
Presentation	Macular and papular rash on chest 1 year after initial diagnosis; pink nodule appeared at 1 year	Nodular skin lesion on right flank (2 months after initial diagnosis)	Initial presentation with bilateral erythematous and nodular ear lesions	Macular and papular rash eruption on chest appeared 11 years after initial diagnosis
Treatment	No treatment after initial diagnosis; rituximab after second skin manifestation	Rituximab and bendamustine after diagnosis; ibritinib after progression	Rituximab due to slow progression of ear lesions	Chemotherapy after initial diagnosis with complete response; skin rash resolved after rituximab and bendamustine
Follow-up	Progression	Progression	Progression	Complete response
Bone marrow involvement	70% (performed at second skin biopsy)	30% (performed at skin biopsy)	5% (performed at skin biopsy)	10–20% (performed at skin biopsy)
M-protein (g/dL)	IgM kappa (0.51)	IgG lambda (1.52)	IgM kappa (0.61 g/dL) and IgM lambda (0.20)	IgM (3.8)

when an IgM serum protein is identified. The costs of these tests should be weighed against those of delayed identification of a more aggressive disease, and the potential side effects (or even increased costs) of a bone marrow biopsy to detect an underlying systemic lymphoid or plasma cell neoplasm.

While the aforementioned symptoms are well recognised features of LPL with Waldenström macroglobulinaemia, cutaneous infiltration is not. Therefore, definite diagnosis of cutaneous LPL, even in the presence of a *MYD88* mutation, should be deferred until SPEP and bone marrow assessment have been performed. The bone marrow biopsy revealed involvement of the bone marrow by LPL in all of our cases (Fig. 2C,D), which also harboured the typical chromosomal aberration of LPL in one case (Fig. 2E).

While the small number of cases described herein constitutes a limitation, they do represent an expansion upon the small number of confirmed reports of cutaneous LPL in the literature. In addition, we offer a detailed description of the histopathological findings, clinical management, and follow-up, and document that progression of the disease (including with cutaneous involvement) is a common feature, warranting early recognition and distinction from other more indolent entities. All cases showed a serum paraprotein of the same light chain subtype, as well as bone marrow involvement by the same neoplastic process. These findings highlight the need for complete haematopathological and clinical assessment of these patients, in order to avoid under-diagnosis of LPL in patients with *MYD88* L265P mutated cutaneous small B-cell lymphomas.

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Isolated IgG4-related cutaneous pseudo-lymphoma with crystal-storing histiocytosis

To the Editor,

IgG4-related disease (RD) is a multi-organ immune-mediated condition that mimics many malignant, infectious and inflammatory disorders.¹ It can present with cutaneous and/or systemic manifestations including IgG4-positive plasma cell organ infiltration with accompanying elevated levels of circulating IgG4.² There are many other fibrosing conditions which are pathologically similar to IgG4-RD.² This poses a diagnostic challenge, and with very limited literature surrounding this rare disease, consistent clinical and demographic history to help guide diagnosis is sparse. Typically, IgG4-RD encompasses middle-aged to elderly males; however, for reasons not yet clear, gender predilection appears to change dependent on the location of the IgG4-RD.¹

Rarer still are isolated cutaneous manifestations of IgG4-RD^{2,3} and in extremely rare instances, cutaneous IgG4-RD can be accompanied by a phenomenon known as crystal-storing histiocytosis (CSH). Very few cases in the literature exist for this entity alone with fewer still for cutaneous IgG4-RD with CSH.⁴

CSH is a rare condition in which crystalline material accumulates within the cytoplasm of macrophages.⁵ CSH can be localised or generalised and, in 90% of cases, is associated with lymphoplasmacytic neoplasms such as multiple myeloma, lymphoplasmacytic lymphoma and monoclonal gammopathy of undetermined significance.⁵ Most of the remaining cases of CSH that are not associated with underlying malignancy appear to show an association with diseases that have an inflammatory background.⁶ The cause of the crystalline deposits is hypothesised to be from histiocytic ingestion of the secreted immunoglobulins which are most commonly kappa light chain, with lambda light chain being a rarer occurrence.^{5,6}

The patient was an 84-year-old male with the only pertinent medical history of a basal cell carcinoma recently excised from his face. He presented to an outpatient clinic for follow up of this excision. On examination a mid-back lesion clinically suspicious for another basal cell carcinoma was