Linear IgA dermatosis in association with angioimmunoblastic T-cell lymphoma infiltrating the skin: a case report with literature review.

Short title: Linear IgA dermatosis associated with an angioimmunoblastic T-cell lymphoma.

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive form of peripheral T-cell lymphoma, characterised by systemic symptoms, diffuse lymphadenopathy, hepatosplenomegaly and immunodysregulation.

Half of AITL is associated with cutaneous symptoms, but only few cases with bullous eruption have been described. Association with a linear IgA dermatosis is extremely rare.

Linear IgA dermatosis can be idiopathic, or linked with drug intake or neoplastic disorders. Some cases of linear IgA dermatosis presenting as toxic epidermal necrolysis (TEN) have been described, most of them being drug induced.

We here present the case of a 72-year-old man recently diagnosed with AITL who developed a bullous eruption, presenting as TEN. Histology showed deep cutaneous involvement of the lymphoma with a sub-epidermal blistering and direct immunofluorescence revealed a heavy IgA linear deposit on the dermal-epidermal junction. A diagnosis of linear IgA dermatosis associated with cutaneous involvement of an angioimmunoblastic T-cell lymphoma was made.

Chemotherapy and corticosteroids allowed cutaneous improvement but the patient died of his lymphoma shortly after.

Case report

A 72-year-old man was admitted to the emergency department for a diffuse eczematiform eruption, associated with a necrosis of the skin of the nose. The day after, he developed large, tense bullae and erosions on the scrotum and the tongue that rapidly spread first symmetrically on the four limbs then on the entire body. The bullous lesions were mostly localised in the great folds (Fig. 1A and 1B). The patient complained about pruritus but no pain. Laboratory studies revealed C-reactive protein at 44 mg/L (Reference range (RR) <5 mg/L), haemoglobin at 8.7 g/dL (RR=13.3-16.7 g/dL), and leukocytes at 18.27x10^3/µL (RR=4.00-10.00x10^3/µL), with 79.5% neutrophils (RR=40-70%) and 8.5% lymphocytes (RR=20-50%). IgA, IgG and IgM levels 2 weeks before admission were within the laboratory reference range (IgA: 3.23 g/L, IgG: 15.1 g/L, IgM: 0.89 g/L, RR respectively 0.70-4.00 g/L,

7.00-16.00 g/L and 0.40-2.30 g/L). Concerning Epstein-Barr virus infection, IgM were negative and IgG were positive (163U/mL).

A diagnosis of bullous drug reaction was made and the patient received oral methylprednisolone. Despite treatment, the blisters rapidly spread, and the oral and conjunctival mucosae were also involved (Fig. 1C). The Nikolsky's sign was positive (Fig 1D). Those symptoms were interpreted as toxic epidermal necrolysis (TEN).

The patient was known for an angioimmunoblastic T-cell Lymphoma (AITL) stage IVBb of Ann-Arbor,[1] with involvement of lymph nodes, spleen and bone marrow. The histology of the lymph nodes had shown T-cell infiltrate of polymorphous small to medium-sized lymphocytes, mostly CD3+, CD4+, CD5+, CD10+, CXCL13+, PD1+, CD20- and PAX5- (Fig. 2). He was treated by CHOP (cyclophosphamide, doxorubicine, vincristine and prednisolone) chemotherapy associated with lenalidomide: he had received the first line of CHOP 3 weeks before admission, along with a 14 days daily intake of 25 mg lenalidomide.

Histology of the eczematiform and necrotic lesions showed a dense dermal and hypodermal infiltrate of atypical lymphocytes, mostly CD3+, CD4+, CD5+, CD4+, CD7- and PD1+ without CXCL13 expression. The infiltrate had a peri-vascular and interstitial disposition. The histological analysis of the bullous eruption showed a subepidermal blistering and a heavy perivascular infiltrate of atypical T lymphocytes and neutrophils (Fig. 3A and 3B). The same clonal TCR gene rearrangement was detected in the bullous lesions and the lymph nodes. On perilesional skin, direct immunofluorescence (DIF) revealed a strong IgA linear deposit on the dermal-epidermal junction, and a weak C3 deposit. No deposition of IgG or IgM was observed (Fig. 3C). A cutaneous involvement of the AITL associated with atypical linear IgA bullous dermatosis (LABD) was diagnosed. The patient received a treatment of gemcitabine associated with intravenous methylprednisolone, which allowed cutaneous improvement but no haematological response. The patient died 2 months after admission.

Discussion

AITL is an aggressive form of T-cell lymphoma. It represents 15 to 20 % of all peripheral T-cell lymphomas, mainly affecting the elderly, with a median age at onset of 65 years. It usually presents with systemic symptoms, generalized lymphadenopathy and often mimics an infectious process. The prognosis is poor, and the median survival is less than 3 years. Cutaneous involvement is one of the most common extranodal expressions of AITL. About half of the patients have cutaneous morbiliform eruption, and most of them experience pruritus. Other common cutaneous involvements include urticaria, purpura, cutaneous nodules, erythrodema and angioedema. Those eruptions could also be linked to drug administration.[2] To the best of our knowledge, 6 cases of blistering skin disease associated with AITL have been previously described,[3-8] with available information for only four of them. These are summarized in table 1. Those six cases presented with various clinical, histological and immunohistochemical aspects: Two cases were AITL with sub-epidermal blistering with linear IgA deposit.[3,4] The third report describes patient with an AITL who developed eroded patches due to an IgA pemphigus.[5] The fourth patient presented an AITL along with purpuric lesions of the lower limbs and the trunk. Histology and direct immunofluorescence revealed an IgA related leukocytoclastic vasculitis. Later, after chemotherapy, he developed large tense bullae of the skin and ulcerations of the oral mucosae, with histology and immunofluorescence of a mucous membrane pemphigoid caused by IgA and IgG antibodies against basement membrane zone.[6] Finally, the last two cases had dermatitis herpetiformis.[7,8] Another case of leukocytoclastic vasculitis with IgA deposit, but without blistering, in association with AITL has also been described.[9] Elevated serum IgA levels appeared to be a prognostic factor in AITL, with poorer prognosis if the level is high. The mechanism of elevated IgA levels is uncertain, but it seems like excessive serum IgA are produced by IgA-plasmablasts induced by neoplastic T follicular helper cells releasing growth factor-β1 and interleukin-21.[10] Other IgA related diseases have also been described in association with AITL, including IgA nephropathy.[11]

In our patient, the LABD seemed to be a paraneoplastic disease occurring when the AITL was worsening, despite an improvement of the skin lesions with corticoids while the AITL did not respond to treatment. LABD associated with AITL could also be linked with drug intake, and in this case the latency period between the CHOP and lenalidomine intake is compatible with

the literature data. However, no case of LABD associated with lenalidomide or thalidomine intake has been previously published. Because of the reported association between AITL and increased IgA levels, and the chronological coincidence between the cutaneous and the haematological conditions, we concluded in our patient that the LABD was a paraneoplastic disease linked to the AITL.

The linear IgA dermatosis associated with neoplasm (LADAN) has the same clinical features than non-neoplastic LABD: grouped papules, vesicles or bullae on a normal or erythematous base, with a symmetric distribution along the extensor side of elbows, knees and buttocks. Mucosal involvement is common. LADAN is most frequently associated with lymphoproliferative malignancies (mainly non-Hodgkin lymphoma and Hodgkin lymphoma), but can also occur with solid tumors, including transitional cell carcinoma of the bladder, esophageal, renal and thyroid carcinoma.[12]

The major differential diagnosis in this case was TEN. LABD presenting as TEN have already been published.[13-19] All reported cases except one[19] could be linked to drug intake. The drug most frequently implicated was vancomycin.

Conclusion

This case report and review of the literature enhance the need of checking adult patients for lymphoma when they present linear IgA dermatosis, especially if the clinical presentation is atypical. It also re-emphases the need for considering LABD in the differential diagnosis of TEN.

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