Bullous Pemphigoid Associated With Mantle Cell Lymphoma

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Background: Bullous pemphigoid has developed in association with different types of malignant diseases, including a few cases of B-cell lymphoproliferative disorders. However, the paraneoplastic significance of this association is still controversial.

Observations: We describe a 39-year-old patient who presented with a bullous eruption and generalized lymphadenopathy. The results of histologic, immunofluorescence, and antigenic studies confirmed the diagnosis of bullous pemphigoid. The histopathologic and immunophenotypic features of a lymph node biopsy specimen were consistent with mantle cell lymphoma. There was total resolution of the mucocutaneous lesions when mantle cell lymphoma went into remission.

Conclusion: The age of the patient and the concomitant appearance and simultaneous remission of both diseases strongly suggest that bullous pemphigoid was a paraneoplastic phenomenon in the present case.

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Bullous pemphigoid (BP), which is an acquired autoimmune subepidermal blistering disorder of the elderly, is characterized by the deposition of IgG and/or C3 along the basement membrane zone (BMZ) on direct immunofluorescence (DIF). Most patients have circulating IgG autoantibodies that can be demonstrated by indirect immunofluorescence (IIF). These antibodies bind to the epidermal side of the BMZ on salt-split skin. Bullous pemphigoid has been associated with different types of malignant diseases, but the paraneoplastic significance of this association is still unclear.1-4

Mantle cell lymphoma (MCL), which is a rare form of non-Hodgkin’s B-cell lymphoma, is derived from a subset of naive pregerminal center cells that are localized in primary follicles or in the mantle zones of secondary follicles. Morphological, immunophenotypic, and molecular features of this type of lymphoma have been well characterized in the last few years, allowing its accurate diagnosis.5,6 Mantle cell lymphoma has a distinctive clinical presentation. It usually affects elderly patients with generalized lymphadenopathy and bone marrow infiltration. Splenomegaly, Waldeyer ring, and gastrointestinal tract involvement are relatively common. Occasionally, patients present with a leukemic phase, which may be misinterpreted as small lymphocytic lymphoma or chronic lymphocytic leukemia. The course of MCL is usually aggressive, with a median survival time of 3 to 5 years. Prognostic factors are not well defined. Increased levels of lactate dehydrogenase and β2-microglobulin, poor performance status, peripheral blood involvement, blastoid variants, and proliferative activity of the tumor have been associated with a poor prognosis.6

The occurrence of autoantibody-mediated skin disease has been rarely reported in B-cell neoplasia, mainly in association with paraneoplastic pemphigus.7 However, immunologic disorders associated with MCL are unusual. We describe a patient who presented with BP associated with MCL. Both diseases had a parallel clinical course, suggesting a paraneoplastic phenomenon.

REPORT OF A CASE

A 39-year-old white man was admitted in February 1999 with a 3-month history of severe odynophagia resulting in 5-kg weight loss and a 6-week history of an extensive eruption of tense blisters and painful oral lesions. His medical history was not relevant, and he was not using any
medications. Physical examination revealed a widespread eruption of tense serohemorrhagic blisters over erythematous plaques, predominantly on the extremities and scattered on the trunk (Figure 1). The Nikolsky sign was negative. The patient also had multiple erosions on the soft palate and floor of the mouth, generalized lymphadenopathy, and mild splenomegaly.

A cutaneous biopsy specimen showed a subepidermal blister with abundant eosinophils in the inflammatory infiltrate. Direct immunofluorescence of a perilesional skin biopsy specimen revealed linear deposition of IgG and C3 along the BMZ (Figure 2), and IIF demonstrated the presence of IgG autoantibodies directed against the BMZ of rabbit lip in a serum sample and in blister fluid. The IgG autoantibodies bound to the epidermal side of 1M sodium chloride split skin, with a titer of 1:640.

On immunoblot analysis, the IgG antibodies from blister fluid reacted with the recombinant NC16A domain of BP180 and showed a faint IgG reactivity against LAD-1 (soluble ectodomain of BP180 obtained from keratinocyte-conditioned medium), and a serum sample showed strong IgG reactivity with LAD-1. A weak reactivity of IgA antibodies from both the blister fluid and the serum sample was also noted with LAD-1. A faint IgG reactivity with a 180-kDa protein was also detected when epidermal and keratinocytes extracts were used as substrate, while no reactivity was observed with BP230. The serum sample and blister fluid were both positive for NC16A reactivity on enzyme-linked immunosorbent assay.

A lymph node biopsy specimen showed a widespread effacement of the nodal architecture, which was replaced by a proliferation of small lymphocytes with scant cytoplasm and irregular nuclei, with persistence of some residual naked germinal centers (Figure 3). Immunophenotypic examination showed the expression of B-cell–associated antigens CD20 and CD79a, with coexpression of CD5 and CD43. The specimen was negative for CD10 and CD23. The neoplastic cells were positive for bcl-2 and IgD and negative for p53. The results of cyclin D1 immunostaining were unsatisfactory, but polymerase chain reaction demonstrated the presence of a bcl-1/JH rearrangement at the MTC locus. The proliferation rate tested with Ki-67 was low (<25%). The results of IIF were negative when the patient's lymph node was used as a substrate.

Laboratory investigations disclosed elevated levels of lactate dehydrogenase (508 U/L [reference range, 250-450 U/L]) and β2-microglobulin (2.9 µg/mL [246 nmol/L]) (reference value, <2.5 µg/mL [<212 nmol/L]). The results of a complete blood cell count and biochemistry profile were within normal limits.

A bone marrow biopsy specimen demonstrated infiltration by MCL. Peripheral blood examination demonstrated 62% malignant lymphocytes, with a CD5+, CD20+, CD23− immunophenotype and λ light chain restriction. Monoclonality was detected by polymerase chain reaction of the complementary determining region III of the heavy chain IgG locus.

A total body computed tomographic scan revealed the involvement of axillary, inguinal, iliac, peripancreatic, and gastrohepatic ligament lymph nodes, with a minimally enlarged spleen. The findings of fibrogastroscopic and fibrocolonoscopic examination were normal.

The patient was started on a regimen of oral prednisone (100 mg/d), with clinical improvement of his cutaneous lesions. When the diagnosis of MCL (stage IVa) was established, he was transferred to the hematology ward. In August 1999, he underwent an allogeneic bone marrow transplantation after cyto reduction with 2 courses of fractionated cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and dexamethasone, which were alternated with high-dose methotrexate and cytosine arabinoside. Cyclosporine was also administered to
patients with BP and negative findings on IIF. The in-
crease and mucosal involvement occur more commonly in
either disease are more common in the elderly.
ported by some authors, whereas others did not find a
relationship between negative IIF findings and malignancy has been sup-
ported by some authors,2,12 whereas others13 did not find a
relationship between negative IIF findings and malignancy. This percentage of cancer incidence is similar to that found by other authors,2,4,10,11 but they believed that the association was to be expected because both diseases are more common in the elderly.
It has been suggested that concurrent malignant disease and mucosal involvement occur more commonly in patients with BP and negative findings on IIF.12 The incidence and clinical significance of mucosal lesions in BP are still uncertain, but the lesions are more common in seronegative patients and do not appear to indicate a worse prognosis or therapeutic response.2 A correlation between negative IIF findings and malignancy has been sup-
ported by some authors,2,12 whereas others13 did not find a relationship between the presence or absence of circu-
latiing anti-BMZ antibodies and the development of mali-
nignancy.
In our case, as in the 3 cases associated with malignancy reported by Muramatsu et al.,14 autoantibodies against BP180 but not against BP 230 were detected. To the best of our knowledge, disease activity correlated with levels of autoantibodies to BP180 NC16A, in contrast to IIF titers,15 but there have been no reports concerning the relationship between autoantibodies against BP180 and internal malignancies.
Venning and Wojnarowska compared the inci-
dence of neoplasia in 84 patients with BP with that in 168 controls. The rate of concurrent BP and malignancy suggested that there was a slight increase in malignancy in patients with BP. They also compared patients with BP with and without neoplasia and only found a preponderance of females in the noncancer group. There were no differences in the prevalence of mucosal involve-
ment, presence of circulating antibodies, or HLA type. The relationship between tumors and BP can be explained by the production of antibodies to tumor-specific antigens that might cross-react with the BMZ. Another hypothesis suggests that tumor cells might se-
crete a substance that could damage the basement mem-
brane, with secondary production of anti-BMZ antibod-
ies. Other theories include the possibility that the same external agent might generate the cancer and the BMZ damage or that there is a genetic predisposition to both diseases.
In B-cell neoplasia, the occurrence of autoantibody-
mediated skin disease has been reported, although rarely and mainly in association with paraneoplastic pemphigus. Araergi et al.17 retrospectively reviewed the DIF results in skin biopsy specimens from 102 patients with B-cell lymphoproliferative disorders and cutaneous lesions. They found 2 cases of typical paraneoplastic pemphigus and 9 cases (8.9%) with linear dermoe-
dermal immunoglobulin or C3 deposition. They analyzed the antigenic specificity of the antibodies in 7 of the 11 cases. One patient had cicatricial pemphigoid, while the others had epidermolysis bullosa acquisita.
There are only a few reports on the association of BP with chronic lymphocytic leukemia, despite the numerous types of dermatologic lesions that can accompany this type of leukemia.18-21 Modiano et al.22 described 1 patient with refractory anemia and an excess of blast cells in transformation and IgM monoclonal gammopathy who developed a subepidermal blistering eruption, with a der-
mal infiltrate of CD13+ and CD15+ cells, showing linear deposits of IgG, IgM, and C3 at the BMZ on DIF exami-
nation. Immunoblotting of the patient’s serum sample revealed IgG antibodies against 3 protein bands: a 210- to 215-kDa band comigrating with desmoplakin 2, a 180-
kDa band comigrating with BP180, and a 190-kDa band. The presence of antidesmoplakin antibodies could be the result of a cellular autoimmune disturbance in a patient with other autoimmune or hematologic diseases. Such antibodies could also be a consequence of the epidermal damage induced by the dermal tumor infiltrate and base-
ment membrane antibodies.22
Bauduer et al.23 described the simultaneous occur-
rence of BP and transformation of a preexisting myelo-
dysplastic syndrome. Misery et al.24 described 1 patient with chronic lymphocytic leukemia and BP in whom both disorders were diagnosed simultaneously. They speculated that BP might be induced by the production of antib-
obies by leukemic B cells, but this hypothesis could not be demonstrated in their study.
Egan et al.24 described 1 patient with BP surrounding an urostomy site (for bladder cancer resection 12 years ear-
lier) associated with a B-cell lymphoma. Although local-
ized BP around a stoma can occur, the coincidental onset of BP and lymphoma in their patient and the regression of tumor mass and clinical improvement of the BP with che-
motherapy also suggest a paraneoplastic phenomenon.
There are striking similarities between common gen-
etic aberrations in MCL and CLL, suggesting that there may be similarities in the pathogenesis of the 2 dis-
eases.6,25-27 Mantle cell lymphoma has a very poor prog-
nosis, but allogeneic hematopoietic transplantation can achieve molecular remissions.26
In our case, the presence of BP allowed the detection of MCL in stage IVa, before the patient’s general condi-
tion had deteriorated, and treatment was undertaken as early as possible. Forty-eight months after the diagno-
sis, the patient was still free of disease. The age of our patient and the simultaneous appearance and remission

Since Lever9 established the criteria for the diagnosis of BP in 1953, many cases associated with malignant dis-
ease have been reported. There has been controversy about whether patients with BP have an increased likelihood of developing an underlying neoplasia compared with age-
matched controls.
Chorzelski et al.1 found that 11% of 110 cases of BP were associated with cancer. They regarded this incidence as highly significant, as they compared with the expectancy of cancer in the Polish population in a corresponding age and sex group. The statistical significance of their find-
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of both diseases strongly suggest that BP was a paraneoplastic phenomenon in the present case.

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REFERENCES