Anti-CD20 Monoclonal Antibody (Rituximab) for Refractory Erosive Stomatitis Secondary to CD20+ Follicular Lymphoma–Associated Paraneoplastic Pemphigus

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 61-year-old white woman was referred in April 1999 with a 6-week history of extremely painful and severe erosive stomatitis accompanied by asthenia, difficulty in eating, and weight loss. Her medical history was unremarkable except for taking atenolol and chlorthalidone for arterial hypertension and hormone replacement therapy. Results of clinical examination revealed fibrin-covered shallow coalescing ulcers on the buccal mucosa, lower labial mucosa, the anterior region of floor of the mouth, and the dorsum and undersurface of the tongue (Figure 1). The initial lesions appeared as red macules followed by erosions. The vermilion of the lips showed extensive erosions and crusting. She also had some isolated 2- to 5-mm erythematous blue maculopapular and slight hyperkeratotic lesions on the palms.

With no improvement after discontinuation of the therapy with atenolol and chlorthalidone and administration of prednisone (60 mg/d for 1 week), a biopsy of a lip lesion was performed. Results of histological examination showed a large inflammatory ulceration covered by a thick layer of fibrin exudate. The underlying fibrous corium contained an inflammatory infiltrate of predominantly lymphocytes located around blood vessels without true vasculitis. The adjacent epithelium was massively spongiotic and penetrated by numerous lymphocytes. Necrosis of individual keratinocytes also occurred (Figure 2).

The rest of the findings from physical examination disclosed a slight enlargement of axillary lymph nodes and the spleen. Results of light microscopy studies of a biopsy specimen obtained from the palm disclosed lichenoid interface changes with some colloid bodies and necrotic keratinocytes scattered through the epidermis. Results of direct microscopy immunofluorescence studies of perilesional lymphocytes located around blood vessels were negative. The patient’s serum immunoprecipitated a 170-kDa protein band from biosynthetically radiolabeled keratinocyte extracts. Findings from laboratory investigations revealed an erythrocyte sedimentation rate of 11 mm in the first hour, a hemoglobin level of 12.6 g/L, a white cell count of 8.2 × 10^9/L, and a platelet count of 255 × 10^9/L. Liver enzyme values, serum creatinine level, and results of urinalysis were normal. Findings from protein immunoelectrophoresis revealed a slight polyclonal hypogammaglobulinemia. A search for antinuclear, anti-DNA, and anticytoplasmic antibodies was negative as were the results of extensive serologic tests, including those for human immunodeficiency virus, human T-lymphotropic virus 1, cytomegalovirus, and herpes simplex viruses.

Viral and fungal cultures remained negative for organisms, while a throat swab yielded Lancefield group A β-hemolytic streptococci. Findings from a chest radiograph disclosed a significant pleural effusion of the right hemithorax. A diagnosis of follicular non-Hodgkin lymphoma grade 1 (according to Revised European-American Lymphoma classification) was established through the results of an axillary lymph node biopsy that demonstrated a nodular lymphocytic infiltration containing CD20+CD79a+, CD5−CD23−, CD43−, and CD10± cells. The Bcl-2 protein was expressed (confirming the diagnosis), while findings for Bcl-1 protein were negative. Finally, the proliferation rate as tested with MiB-1 was 5% to 10%.

Findings from a total-body computed tomographic scan revealed involvement of all deep lymph node areas with bulky lesions in the mediastinum and in the retroperitoneum. Left pleural effusion findings were positive for tumor cells, and bone marrow infiltration was present. The stage of the disease was IVA. The patient received 6 courses of standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. Tumor response was evaluated after 3 cycles of CHOP with partial response noted. After 6 cycles, mediastinal lesions resolved, but pleural effusion and a residual retroperitoneal mass remained. The stomatitis showed only slight improvement.
Our patient presented with an erosive stomatitis and lichenoid lesions on the palms, the clinical and immunopathological features of which were characteristic of paraneoplastic pemphigus (PNP). Evaluation for an occult neoplasm led to the discovery of a follicular B-cell lymphoma. In PNP related to malignant neoplasias, involvement of oral mucosa is distinctively refractory to all treatments. In our patient, high doses of prednisone, cycles of chemotherapy, and various topical treatments (including mouthwashes with antibiotics, cyclosporin, 0.5% retinaldehyde, and sucralfate) had little effect on her oral disease.

SOLUTION

In an attempt to better control the lymphoma, 375 mg/m² of a monoclonal anti-CD20 antibody (rituximab) was given once a week for 4 weeks. Two phase 2 trials have validated this treatment in relapsing follicular lymphoma. With this regimen residual lesions shrank, and after 2 months of observation, excellent partial tumor response was observed. Strikingly, the mouth lesions rapidly improved with reepithelization of most mucosa within 4 weeks (Figure 3). Maintenance therapy consisted of 375 mg/m² of rituximab once every 2 months. After 3 months only a small erosion on the tongue was present, and she regained her weight. There were no signs of tumor progression. The therapeutic regimen with rituximab was well tolerated.

COMMENT

Paraneoplastic pemphigus is an autoimmune mucocutaneous disorder associated with an underlying neoplasia. Its diagnosis is based on the following criteria: (1) presence of mucosal lesions with intractable stomatitis together with a polymorphous skin eruption, the features of which might be similar to those of pemphigus vulgaris, erythema multiforme, bullous pemphigoid, and/or lichen planus; (2) variable histological findings, including acantholysis, dyskeratotic keratinocytes, and lichenoid and vacuolar interface changes; (3) immunopathologically, faint and focal deposits of IgG and C3 in the intercellular space and along the basement membrane zone of the affected epithelial tissues; (4) identification of circulating autoantibodies binding to stratified as well as nonstratified epithelia; and (5) a mostly identifiable immunoprecipitated complex of proteins in the serum samples from affected patients. The target antigens belong to the plakin family of intermediate filament binding proteins, including plectin, desmoplakin I and II, the bullous pemphigoid antigen 230, envoplakin, and periplakin. In addition, PNP sera frequently contain autoantibodies directed against the desmosomal components desmoglein 3 and desmoglein 1.

Finally, as in our patient, an uncharacterized protein of 170 kDa is almost invariably immunoprecipitated.2

The neoplasias in PNP include predominantly non-Hodgkin lymphoma, chronic lymphocytic leukemia, and, less frequently, Castleman disease, thymoma, and reticulum cell sarcoma. While patients with thymoma or Castleman disease frequently exhibit a considerable improvement on surgical excision of the tumor, the prognosis of patients with PNP with a malignant neoplasia is poor.2 In a group of 84 patients with PNP, the mortality...
rate was estimated at more than 90%. Anhalt reported that most patients with both PNP and malignancies die 1 month to 2 years after diagnosis with complications related to either the immunosuppressive treatment or the syndrome. Besides infection and multiorgan failure, respiratory insufficiency with features characteristic of bronchiolitis obliterans is a common cause of death. 

Patients with PNP generally have benefited from high doses of oral corticosteroids, which result in an improvement of the cutaneous lesions without significant effect on oral involvement. Immunosuppressive therapies (including azathioprine, cyclosporin, dapsone, and photopheresis) have been tried in single cases with variable and inconsistent effects. Significant responses have occurred with high doses of cyclophosphamide in combination with prednisone or cyclosporin. A regimen consisting of mycophenolate mofetil, azathioprine, and prednisone resulted in a slow but gradual improvement of mucocutaneous lesions in a recently described patient. Fludarabine was found to worsen or even trigger the course of PNP.

Rituximab is a specific mouse and human chimeric monoclonal antibody. This IgG1κ with a half-life of 76 to 200 hours targets the CD20 antigen, a phosphoprotein of 297 amino acids expressed on the surface of pre-B and B lymphocytes as well as on malignant B cells. Rituximab has shown high efficacy in the treatment of relapsing and refractory follicular lymphoma. In addition, responses have occurred in relapsing high-grade lymphoma. Compared with chemotherapy, this new therapeutic weapon has the main advantage of having a very low toxicity profile. Mild allergic reactions, such as fever and chills, occur during the first infusion. Maintenance treatment as used in our patient is still experimental. Although a recent multicentric Swiss trial questions rituximab’s efficacy, we thought that our patient could benefit from such a regimen because of her special clinical condition.

Passive transfer experiments have indicated that autoantibodies from patients with PNP are pathogenic in vivo. However, the exact mechanism by which they cause widespread tissue damage remains unclear. The plakins are entirely cytoplasmic proteins; hence their implication as autoantigens in disease initiation seems unlikely. The role of autoantibodies to the uncharacterized 170-kDa protein is unknown. Autoantibodies directed against desmoglein 3 and desmoglein 1 most likely contribute to loss of cell adhesion and blister formation. However, the involvement of tissues (such as respiratory epithelium) that do not express desmoglein 1 and desmoglein 3 or the 170-kDa target antigen suggests that additional inflammatory mechanisms are implicated. Elevated serum levels of interleukin 6, which affects differentiation and maturation of both B and T cells, have occurred, particularly in patients with an aggressive clinical course. Recently, evidence has been provided supporting the idea that cytotoxic T lymphocytes with a graft-vs-host disease–like phenotype and apoptotic keratinocyte death contribute to epithelial damage. In our case, it is conceivable that the anti-CD20 treatment had a critical impact on the immune response by means of a reduction of either the malignant or normal B-cell population. Although it is possible that the improvement of the stomatitis in our patient was related to the concomitant regression of the lymphoproliferative disease, it has been pointed out that there is no clear correlation between the evolution of mucocutaneous features and both the burden and treatment of the underlying malignant disorder.

In conclusion, the observation that use of anti-CD20 antibodies for follicular non-Hodgkin lymphoma resulted in a rapid improvement of the severe stomatitis in our patient with PNP suggests that this treatment constitutes an interesting therapeutic alternative for PNP without the serious adverse effects associated with standard immunosuppressive agents. This idea is supported by a similar striking response to rituximab in another case of PNP associated with follicular non-Hodgkin lymphoma (oral communication of M. Heizman, MD, and M. J. Bargetzi, MD, May 2000). Because of the usual resistance of PNP to any form of treatment and its poor prognosis, rituximab therapy deserves further investigation in this mucocutaneous disease when associated with neoplasms and lymphoproliferative disorders other than CD20+ non-Hodgkin lymphoma.

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REFERENCES


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