CD20⁺ cutaneous T-cell lymphoma with phenotypic shift after treatment with rituximab: Case report and review of the literature

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INTRODUCTION

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma (CTCL), classically expresses a typical, post-thymic, CD4⁺ immunohistochemical phenotype, (CD5⁺/CD4⁺/CD45RO⁺ with frequent loss of CD7). However, variations in antigen expression do occur, and T-cell lymphomas involving the skin aberrantly expressing the CD20 antigen have drawn recent attention, variably classified as peripheral T-cell lymphoma, not otherwise specified, MF, and primary cutaneous CD4⁺ small/medium-sized T-cell lymphoproliferative disorder. Here we report an aggressive case of CD20⁺ MF that clinically failed to respond to the anti-CD20 agent, rituximab, despite loss of CD20 expression in persistent lesions.

CASE REPORT

A 66-year-old, obese man with a history of papillary thyroid carcinoma status-post thyroidectomy and radioiodine ablation, diabetes mellitus type II, and hypertension, presented with a tumor on his right anterior neck slowly enlarging for the last 7 months (Fig 1, A). Approximately 2 months after its appearance, biopsy of the neck mass found CD3⁺/CD20⁺ T-cell lymphoma, suspicious for folliculotropic MF (Fig 1, B-D). The patient also reported a 3- to 4-year history of symmetric, itchy, ovoid lesions of the bilateral axillae, waist, and flanks unresponsive to a combination of clotrimazole and betamethasone, although triamcinolone relieved pruritus.

On presentation to our clinic, biopsies of both the neck tumor and a left chest wall patch, each revealed an atypical lymphocytic infiltrate featuring folliculotropism and epidermotropism with Pautrier microabscesses. Immunohistochemical studies found the atypical lymphocytes to be positive for CD3 and CD4, with very few cells highlighting for CD79a and CD8. CD20 staining was remarkably intense, colocating with approximately 80% of the CD3⁺ cells. A monoclonal T-cell population was identified on the neck tumor using T-cell receptor γ primers according to the BIOMED-2 protocol. Flow cytometry of peripheral blood and bone marrow detected no evidence of lymphoma. Positron emission tomography/computed tomography scan showed an intensely hypermetabolic right anterolateral neck mass and mild-to-moderately hypermetabolic right cervical level IIB, right superficial intraparotid, pancreaticoduodenal, and left inguinal lymph nodes suggestive of additional disease. Results of laboratory investigations including lactate dehydrogenase, serum electrolytes, and complete blood count with differential were within normal limits.

A rituximab course was initiated, infused weekly for 4 consecutive weeks at a dose of 375 mg/m² (1,000 mg at each infusion). Unfortunately, the tumor and patch/plaque stage disease showed minimal response, prompting administration of liposomal...
doxorubicin at 40 mg/m² (102 mg at each infusion) every 4 weeks. Despite 2 infusions of doxorubicin, notable tumor growth necessitated use of involved-field radiation therapy at a dose of 36 Gy in 18 fractions. Significant improvement in the tumor was achieved postradiation, but there was concurrent progression of the patches and plaques; thus, 3 cycles of romidepsin with adjuvant topical nitrogen mustard ointment therapy was administered, with no response.

A repeat biopsy of a left chest wall plaque (in the same region as the initial patch biopsy) demonstrated an epidermotropic lichenoid infiltrate of medium-to-large, pleomorphic atypical CD3⁺ T-lymphocytes with cerebriform nuclei. Only very rare CD20⁺ lymphoid forms were identified, in contrast to the previous biopsy specimens, which showed the majority of CD3⁺ cells to also express CD20. Because this biopsy was taken 9 months after the rituximab course, the possibility of false-negative CD20 immunohistochemical staining caused by rituximab occupation of the CD20 antibody generator (which may last for up to 6 months after administration) was excluded. T-cell clonality studies detected the identical clone identified on the previous biopsy 11 months prior. Gemcitabine was initiated, resulting in significant improvement in all skin lesions after 2 cycles. After 4 cycles, most skin lesions continued to improve; however, enlargement and ulceration were noted in the left chest wall/
axillary tumor. Despite a repeat course of involved-field radiation therapy at a dose of 36 Gy in 18 fractions, Positron emission tomography/computed tomography scan showed additional disease of the face, left latissimus dorsi, and bilateral inguinal lymphadenopathy. A bendamustine trial was unsuccessful, prompting switch to multitagent chemotherapy with 2 cycles of EPOCH (etoposide, prednisone, vincristine [Oncovin], cyclophosphamide and doxorubicin hydrochloride [hydroxydaunorubicin hydrochloride]). He soon died of progressive disease.

DISCUSSION

Recognition that subsets of primary cutaneous T-cell lymphomas can express CD20 is an emerging concept. Analysis of 311 transformed MF cases from the French Cutaneous Lymphoma Study Group registry found 148 cases to exhibit at least some CD20 positivity, but only 6 represented aberrant expression in T cells.1-5 To date, 20 cases of CD20+ primary CTCL have been reported,1-10 previously categorized as MF, primary cutaneous peripheral T-cell lymphoma, or simply as peripheral T-cell lymphoma not otherwise specified, according to the current World Health Organization/European Organisation for Research and Treatment of Cancer classification scheme. Distinction from a B-cell neoplasm exhibiting aberrant T-cell immunophenotypic markers can be challenging, but, as in our patient, the constellation of epidermotropism and folliculotropism, T lymphocyte clonality, and persistence of clinical lesions with persistent T-cell markers despite loss of B-cell markers, all support the diagnosis of T-cell lymphoma.

As a transmembrane glycosylated phosphoprotein, the cell surface antigen CD20 is expressed in the early stages of B-cell development before differentiation into plasma cells.6 It is hypothesized that CD20+ MF may derive from the CD20-expressing subset of non-neoplastic T lymphocytes of peripheral blood, as suggested by frequent CD8 coexpression.1 Moreover, CD20 expression in CTCL may reflect activation or acquisition during malignant transformation,1 as supported by the correlation of CD20 expression with advanced stages of CTCL.9 From a cutaneous standpoint, these advanced stages are manifested by enrichment for nodules and tumors over patches and thin plaques in cases of CD20+ MF. As a monoclonal human-mouse chimeric antibody to CD20 cell surface molecules on lymphocytes, rituximab would seem an attractive treatment option; however, in addition to the lack of effectiveness in our patient, 2 other cases in the literature document similar lack of efficacy: the posterior thigh CD20+ TCL tumor nodules of a 65-year-old woman relapsed after rituximab therapy,2 and the disseminated skin, lymph node, and bone marrow involvement by CD20+ TCL of an 83-year-old woman did not respond to 1 cycle of R-ESHAP (rituximab plus etoposide, methylprednisolone, cytosine arabinoside, and platinum).10

Our patient’s remarkable clinicopathologic presentation, treatment, and course contribute valuable added experience to the few existing reports that characterize CD20+ MF. Our patient’s large neck tumor with background-scattered plaques corroborates prior clinical description of CD20+ MF as associated with more substantive cutaneous lesions and advanced-stage disease. From a histopathologic standpoint, along with diffuse atypical lymphoid infiltrates with epidermotropism, folliculotropism was highlighted by our patient’s lesions, possibly representing an adverse prognostic sign. Finally, despite near-complete eradication of the CD20+ lymphoid population in lesional skin, targeted therapy with rituximab was unable to induce remission, with persistence of the T-lymphocytic clone, necessitating further search for alternative treatment options for this unusual condition.

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