Primary cutaneous low-grade B-cell lymphoma treated with hydroxychloroquine

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INTRODUCTION
Primary cutaneous B-cell lymphoma is an uncommon type of non-Hodgkin lymphoma whose primary site involves the skin. Most subtypes of this lymphoma are low-grade malignancies that follow an indolent course and confer good prognosis. Here, we report a novel treatment of a low-grade cutaneous B-cell lymphoma showing complete response to hydroxychloroquine.

CASE REPORT
A 68-year-old man presented to his general practitioner with a violaceous nodule on the right aspect of the scalp. The patient had a medical history significant for hypertension, dyslipidemia, and a herniated disc. Before presentation at our institution, a biopsy from the right side of the forehead was performed, but provided inconclusive results and a differential diagnosis that included lupus. The pathology report could not be successfully obtained from the patient's records. Blood test results, conducted at that time, did not support a diagnosis of lupus. In accordance with the pathology report alone, for a presumed diagnosis of lupus, the patient began receiving hydroxychloroquine 200 mg twice daily for 2 months, and the lesion resolved and treatment was stopped. Several years later, he presented with several similar plaques on the scalp and was prescribed hydroxychloroquine by his family physician, with similar results. When he had a new lesion 12 years after the initial diagnosis, he was referred to the dermatology service. A repeated biopsy was performed from the scalp and was indicative of a low-grade B-cell lymphoma, favoring cutaneous marginal-zone lymphoma.

The biopsy showed a nonepidermotropic full-thickness dermal infiltrate of lymphoid cells with slightly irregular nuclear contours and low Ki-67 labeling. Immunophenotyping revealed a PAX5-, CD20-, and Bcl-2–positive B-cell population, with weak patchy Bcl-6 and MUM-1 positivity. CD3 and CD5 labeled associated T cells. CD10, CD23, CD15, CD30, CD43, and cyclin D1 results were negative. c-Myc result was positive in less than 5% of the B-cell population. Clonality studies to further classify the lesion were not available. Based on the predominantly B-cell immunophenotype and low Ki-67 labeling, the diagnosis of a low-grade B-cell lymphoma favoring cutaneous marginal-zone lymphoma was made. A complete blood cell count revealed a normal leukocyte, lymphocyte, and hemoglobin level. The patient had mild thrombocytopenia, with platelet levels at 113 (×10⁹/L), which had been stable for 3 years. Staging for extracutaneous involvement with a full-body positron-emission tomographic scan did not reveal any lymphadenopathy or areas of hypermetabolism. The spleen was slightly enlarged. There was a nonspecific hypermetabolic process in the medial aspect of the right eyelid. The patient was referred to ophthalmology for an examination and orbital ultrasonography, results of which were normal. Antinuclear antibody testing results were negative, and as a result, at our institution extractable nuclear antigen antibody test was not performed.

Table I summarizes the patient’s various presentations and response to treatment. After his second...
visit to dermatology, the patient requested repeated treatment with hydroxychloroquine because this had worked previously. After 3 months of treatment, the lesions resolved. The following year, he presented to our dermatology service for a recurrence to the right side of the scalp. Physical examination revealed a 2 × 2-cm smooth violaceous plaque on the right side of the scalp that was again morphologically similar to his previous plaques (Fig 1, A). No lymphadenopathy was noted on examination. The patient requested repeated treatment with hydroxychloroquine 200 mg orally twice daily because there

Table I. Clinical features of the initial and subsequent presentations of the patient

| Patient and treatment characteristics | Initial presentation to dermatology | Second presentation to dermatology | Third presentation (initial visit to our clinic) |
|--------------------------------------|------------------------------------|-----------------------------------|------------------------------------------------|
| Age, y                               | 56                                 | 68                                | 69                                              |
| Morphology of lesion                 | No access to documents             | Smooth violaceous papules and plaques | 2 × 2-cm smooth violaceous plaque               |
| Location of lesion                   | Right side of scalp               | Right side of scalp              | Right side of scalp                             |
| Histology                            | No access to histology             | Full-thickness dermal infiltrate of lymphoid cells with slightly irregular nuclear contours | Not performed                                   |
| Immunohistochemical Profile          | PAX5⁺, CD20⁺, Bcl-2⁺ and MUM-1⁺\text{Ki-67 in <10\% c-Myc in <5\%} | Pathologic diagnosis: low-grade B-cell lymphoma, favor cutaneous marginal-zone lymphoma | Not performed                                   |
| Treatment, HCQ 200 mg PO BID, mo     | 1                                  | 2                                 | 3                                               |
| Time to treatment response           | Clear at 1 mo                      | Clear within 2 mo                 | 90\% improved at 6 wk                           |
|                                      |                                     |                                   | 100\% clear at 12 wk                            |
| Time to relapse                      | Recurred several times in different places in the scalp in 12 y, each time responding to the same dose of HCQ within 1−2 mo | Recurred after 1 y                 | Recurred after 8 mo. Restarted HCQ and almost clear at 1 mo. |

\textit{BID,} Twice daily; \textit{HCQ,} hydroxychloroquine; \textit{PO,} orally.

\textbf{Fig 1.} Recurrent primary cutaneous low-grade B-cell lymphoma presenting in a man aged 68 years. Violaceous plaque on the scalp (A) that had previously been biopsied. The patient was treated with hydroxychloroquine 200 mg twice daily for 3 months and followed up at 6 months, with no evidence of the lesion (B).
was no evidence of systemic lymphoma and he had previously tolerated the medication well, with good treatment effect. He was aware that this was not the standard treatment for cutaneous B-cell lymphoma. There was rapid improvement within 6 weeks of initiating hydroxychloroquine. He continued this treatment regimen without adverse effects or signs of toxicity and experienced complete resolution at 3 months and subsequently stopped his medication. At 6-month follow-up, there was no evidence of recurrence (Fig 1, B). The lesion recurred after 8 months and again was treated with hydroxychloroquine 200 mg twice daily and was almost clear at 1 month. We recently contacted the patient, 2 years after his last treatment, and he has not had any recurrence of the lesions.

**DISCUSSION**

There is often difficulty in accurately diagnosing cutaneous lymphomas because there are overlapping clinical and histologic features with other inflammatory dermatoses. Immunophenotyping and molecular studies are helpful adjuncts for establishing the correct diagnosis.

The patient began receiving hydroxychloroquine initially because of a misdiagnosis on histology, but nevertheless he had great benefit from this medication. The exact mechanism of action of antimalarial drugs is not fully elucidated, but hydroxychloroquine is thought to have anti-inflammatory, immunosuppressive, and antineoplastic effects. Antimalarials have long been used to treat a variety of lymphocytic infiltrative dermatoses such as pseudolymphoma and lupus. They have also been shown to concentrate within lymphatic tissue. Hydroxychloroquine may suppress lymphocytes, which could result in clinical improvement of lymphocytic infiltrating diseases. Hydroxychloroquine has also been shown to inhibit autophagy and is being studied as a potential therapeutic cancer agent in combination with chemotherapy. Antimalarials were used as malaria prophylaxis in Tanzania and a subsequent reduction in the incidence of Burkitt lymphoma was noted. They were also shown to prevent B-cell lymphoma in mice models of human Burkitt lymphoma and ataxia telangiectasia. In an extensive literature review, there was only 1 case report of a pleomorphic CD8+ cutaneous T-cell lymphoma responding to hydroxychloroquine.

Many low-grade B-cell lymphomas presenting on the scalp of men are primary cutaneous follicular-cell lymphomas, which typically have a different staining pattern than in our patient; specifically, a positive Bcl-6 and negative Bcl-2 result. B-cell lymphomas have slightly different staining profiles, which contributes to reduced diagnostic accuracy, especially given this infrequent diagnosis for dermatopathologists.

This case presents a novel use of hydroxychloroquine for the successful treatment of an indolent cutaneous B-cell lymphoma. Vigilant follow-up is required to ensure that progression to a higher-grade lymphoma is not missed. Hydroxychloroquine may offer a noninvasive, relatively safe, fast-acting therapeutic option for primary localized low-grade B-cell lymphomas.

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