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Cutaneous Disease as a Rare Presentation of Follicular Lymphoma Progression

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Abstract

Follicular lymphoma, the third most common lymphoid malignancy, is considered indolent but incurable non-Hodgkin lymphoma. Isolated cutaneous relapse from follicular lymphoma is very uncommon, and very few cases have been reported in the literature. In this article, we present a case of an adult patient with a history of treated follicular lymphoma who presented with a skin lesion on his face and scalp. Further workup, including biopsy, led to the diagnosis of relapsed follicular lymphoma with no progression of disease elsewhere. We reviewed cases of follicular lymphoma, which relapsed with isolated cutaneous involvement. Treatment options for relapsed follicular lymphoma include observation, anti-CD 20 antibody alone, or in combination with chemotherapy, radio-immunotherapy, and stem cell transplantation in selected patients. Increased awareness of disease evolution and prompt diagnosis of this form of relapse from follicular lymphoma will improve the effectiveness and outcome of its management.

Keywords

follicular lymphoma, cutaneous

Introduction

Follicular lymphoma is considered an indolent but incurable non-Hodgkin lymphoma. It is the third most common lymphoid malignancy.[1] Isolated cutaneous relapse from previously treated follicular lymphoma is a rare manifestation. We present a case of an adult patient with a history of previously treated follicular lymphoma who presented with a skin lesion. Usually cutaneous involvement by systemic lymphoma is easy to recognize as it manifests as rapidly growing and dull red to violaceus plaques/nodules. His skin lesions were in the form of subtle induration which is unusual for cutaneous involvement by systemic lymphoma.

Case Presentation

We present a case of a 64-year-old Caucasian male with a medical history considerable for chronic obstructive pulmonary disease and traumatic brain injury presented with worsening right inguinal area swelling for the past 5 years. The patient was asymptomatic otherwise. A computed tomography (CT) scan of the abdomen and pelvis was obtained first time in 2015, which demonstrated pelvic and abdominal lymphadenopathy. He was referred to surgery for an excisional biopsy, which revealed follicular lymphoma World Health Organization Grade I-II (Figure 1). Fluorescence in situ hybridization (FISH) was positive for IGH/BCL2 translocation *t(14;18)*(q32;q21). It was negative for MYC/IGH translocation and BCL6 rearrangement. It was determined at the time of diagnosis that the optimal therapy would be observation. One year later, the patient complained of generalized weakness as well as difficulty urinating due to obstructive uropathy secondary to lymph nodes that were identified on a CT scan of the abdomen and pelvis. Bone marrow biopsy was performed at that time and was positive for follicular lymphoma involving bone marrow (Figure 2). Morphology and flow cytometry were positive for 20% involvement by follicular lymphoma cells. Flow cytometry showed a large population of CD19-positive cells that co-express CD10. Neoplastic lymphocytes were positive for CD20 and expressed a kappa surface light chain in a restricted fashion. The FISH was positive for IGH/BCL2 translocation. After a discussion with the patient, he was given 4 weekly doses of rituximab in 2016, with subsequent CT scans showing an almost

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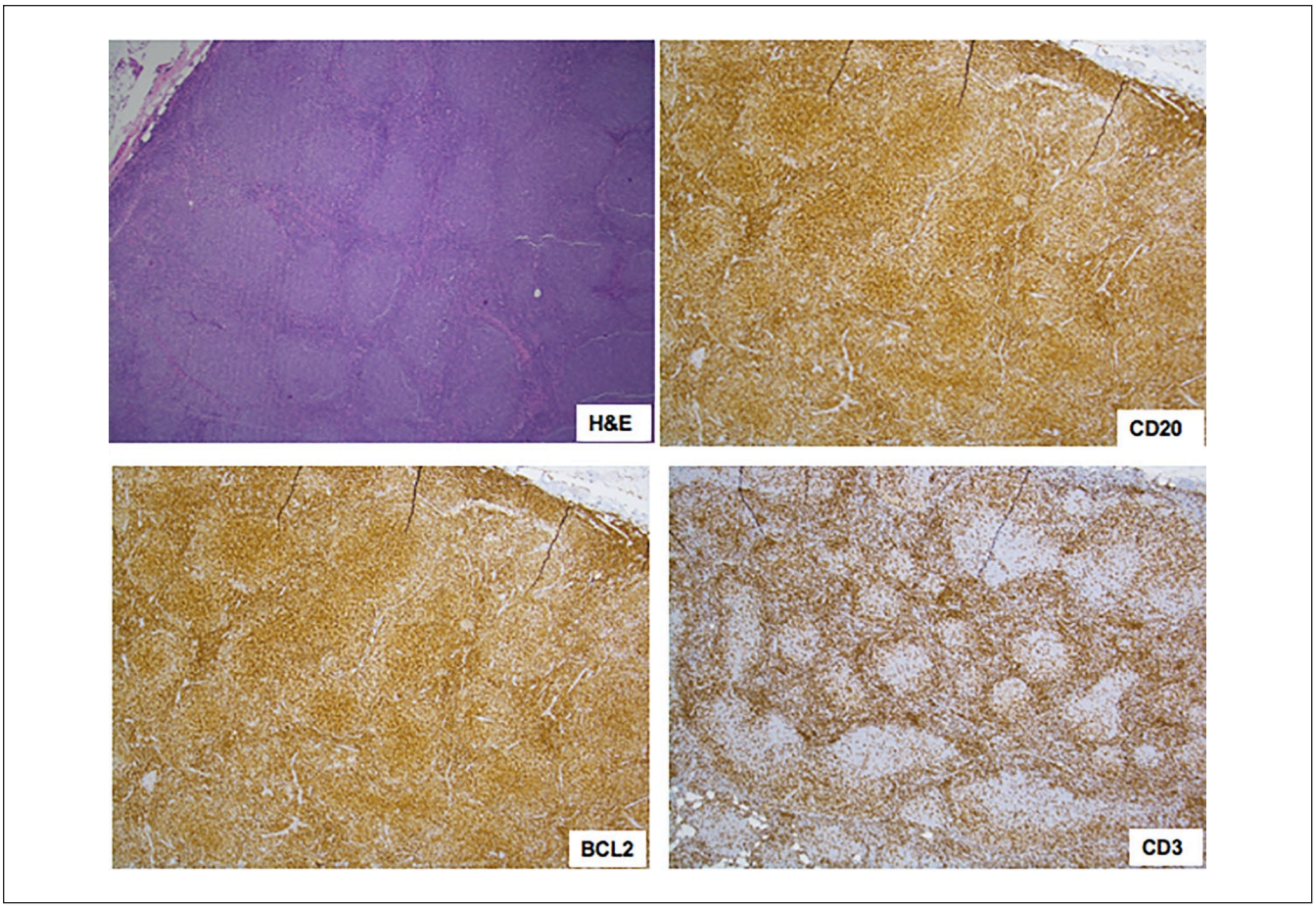

Figure 1. Lymph node. Hematoxylin-eosin, 40× magnification shows follicular lymphoma of an effaced lymph node with closely packed uniform follicles with attenuated mantle zones. The lymphocytes within the follicles are small mature centrocytes. The lymphoid follicles are positive for CD20 and BCL2. The follicles are negative for CD3. CD3 highlights the diminished paracortical zones.

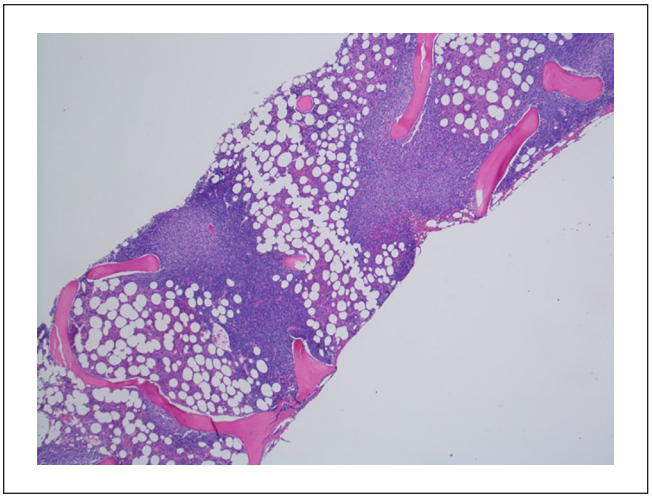

Figure 2. Bone marrow. Hematoxylin-eosin, 40× magnification, shows normocellular bone marrow with paratrabecular nodular lymphoid aggregates comprising ~20% of the marrow cellularity. The lymphocytes are kappa clonal B-cells by flow cytometry and express the following markers: CD10, CD19, and CD20.

40% reduction in the size of the lymph nodes involved. Given some response and resolved obstructive uropathy, the patient was again placed under active surveillance with laboratory results and serial imaging to monitor for any relapse. He also had comorbidities and it was decided to hold off on any systemic treatment. During that period, the patient's case was further complicated by an upper extremity deep vein thrombosis requiring oral anticoagulation as well as a lower extremity fracture requiring surgical repair. He also developed multiple squamous cell carcinomas (SCCs) of the face treated with local excision around 6 months after completion of rituximab therapy. There were no cell count abnormalities, B-symptoms, or radiological evidence of disease progression.

Two years after the patient received rituximab, he underwent Mohs microscopic surgery to remove a lesion on the right side of the face. The biopsy contained evidence of both SCC and follicular lymphoma (CD20+, CD10+ with BCL2 rearrangement by FISH) and no evidence of large cell transformation. Positron emission tomography (PET)/CT was done in November 2018, which was compared with

PET/CT done in September 2016 before first treatment. It showed the abdominal lymph nodes with some response from prior therapy, findings were still consistent with improvement compared with prior scans; however, on current PET/CT scan, there was new abnormal uptake on the left side of the scalp and soft tissue density along with the anterior right submandibular gland. There was uptake along left lateral scalp where there is scalp thickening measuring 10 mm with maximal SUV of 8.3. There was soft tissue density along anterior right submandibular gland which measured 1.5 × 1.9 cm and there was maximum SUV of 6.0. There was hypermetabolic activity within retroperitoneum with maximum SUV 10. This measured 2.4 × 3.0 cm and was previously larger and there was more extensive involvement. There were hypermetabolic lymph nodes in right common femoral region. Lymph node had maximum SUV 11.6 and the largest lymph node measured 1.9 × 1.6 cm. Previously there was more extensive lymphadenopathy in this location.

Given the new relapse involving extranodal sites, the patient was offered systemic therapy with rituximab and bendamustine. He ultimately refused chemotherapy and was treated again with 4 cycles of rituximab in January 2019. Interval PET/CT in April 2019, 8 weeks after therapy suggested complete response to treatment with resolved abdominal lymphadenopathy as well as improvement in the lesion of the right side of the patient's scalp. As compared with previous PET/CT in November 2018, paraortic and bilateral iliac lymphadenopathy had resolved. There was no abnormal hypermetabolic focus in abdomen and pelvis and no abnormal hypermetabolic activity was seen in the neck.

Three months later, he again developed swelling on the left side of his face (Figure 3). A biopsy was obtained and found positive for low-grade follicular lymphoma, Grade I-II (Figure 4). FISH was positive for translocation t(14;18)(q32;q21)/IGH-BCL2 rearrangement, consistent with the relapse. The patient was referred to radiation oncology for palliative radiation as he was initially refusing chemotherapy. Another PET/CT scan demonstrated skin thickening in the facial area, neck, scalp, and upper thorax with no evidence of disease elsewhere (Figure 5). Given the extent of illness, he was not deemed an appropriate candidate for radiation therapy. Accordingly, he agreed to be treated chemo-immunotherapy. The patient was started on bendumastine and rituximab. He had a good clinical response with improvement in his skin lesions.

Figure 3. Figure shows large arrow as biopsy site. It has thick induration, which was biopsied as follicular lymphoma. The patient has fair skin phototype and clear signs of chronic solar damage (clearly observable in the neck area). Two asterisks showed possible actinic keratosis/squamous cell carcinomas.

Discussion

Follicular lymphoma is a prevalent B-cell malignancy characterized by sluggish growth patterns and frequent relapses. Almost 13960 cases of follicular lymphoma in United States were reported in 2016, making it the third most common lymphoid malignancy after diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia or small lymphocytic lymphoma. Incidence has been stable since the last decade.[1] The most common presentation of follicular lymphoma is asymptomatic lymphadenopathy that waxes and wanes for years. Bone marrow involvement is commonly seen in 70% of cases. Other sites of involvement are less common.[2]

There have been reported cases where non-Hodgkin lymphoma exclusively relapsed in the skin, but trials with follicular lymphoma have very rarely reported the cutaneous manifestation.[3] Some of the cases described in the literature are mentioned in Table 1. Relapse occurred at the cutaneous site in our case, which was not involved primarily with no evidence of disease progression elsewhere.

One of the fascinating thing in our case is the predominant deep dermal/subcutaneous involvement with clear sparing of the upper dermis. Usually, cutaneous involvement in systemic B-cell lymphomas is easy to recognize, as it appears with rapidly growing, dull red to violaceus plaques/nodules,[4] while in this case is a subtle pinkish induration of the face (Figure 3). Other differentials of his skin manifestation included rosacea and pseudolymphomas. It is evident from our reviewed cases that none of the patients presented like our patient (Table 1).

Skin lesions in the patient with a previous history of follicular warrants biopsy. Although rare, transformation

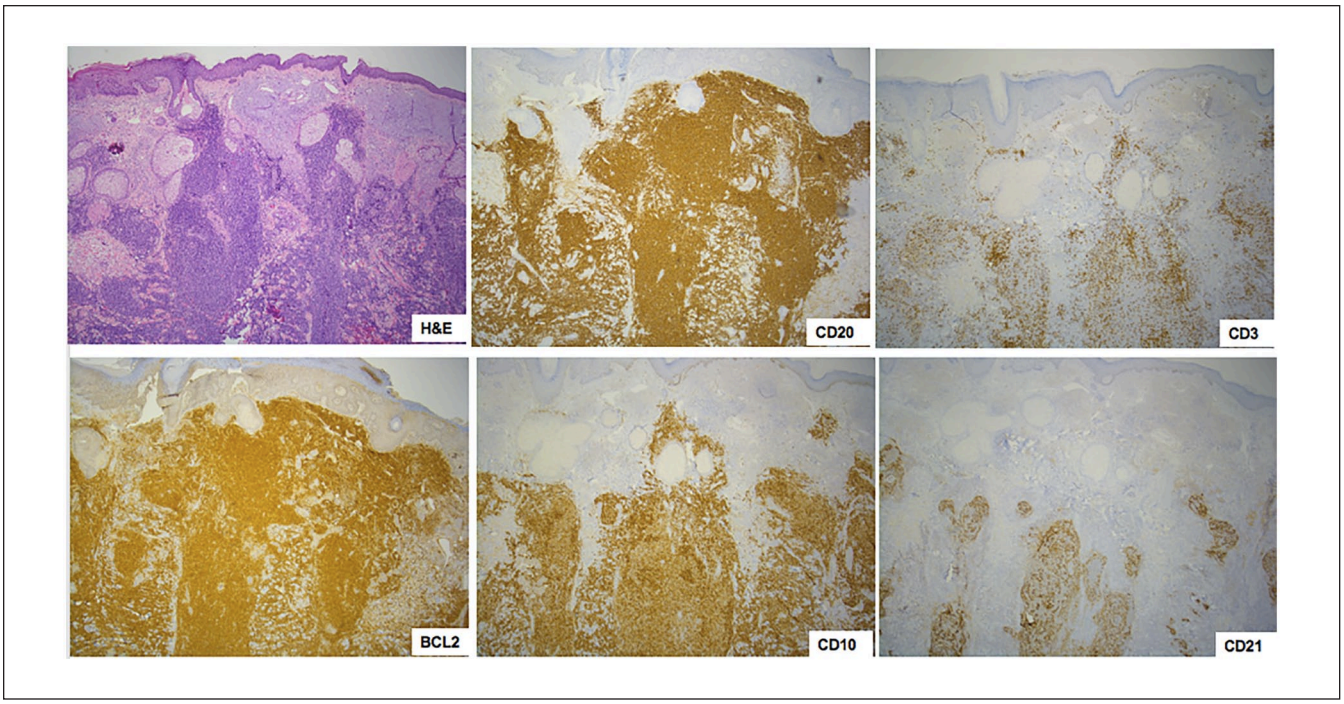

Figure 4. Follicular lymphoma of the face. Hematoxylin-eosin show the preservation of epidermis and papillary dermis. The reticular dermis and underlying deep subcutaneous tissue show an atypical nodular infiltrate of small cleaved lymphocytes. The atypical lymphoid infiltrate is positive for CD20 and co-expresses BCL2 and CD10. CD21 shows disruption of the follicular dendritic mesh network. CD3 is positive in background scattered T-cells.

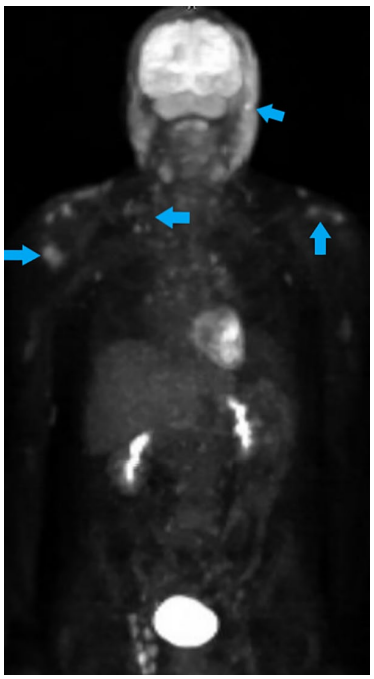

Figure 5. Positron emission tomography-computed tomography scan showing areas of skin thickening on the face, scalp, neck, upper chest, and shoulders (blue arrows). No other areas of abnormal uptake is observed.

to DLBCL as well as double hit B-cell lymphoma have been reported and will affect the management of the disease.[5,6] Treatment of follicular lymphoma depends on the stage and grade of the disease. For localized disease, radiation is an effective option. In patients with the disseminated disease who are asymptomatic and have no cell count irregularities or end-organ damage, observation is a reasonable option. In symptomatic patients, treatment with anti-CD20 antibody with or without chemotherapy is recommended. Most of the patients have a good response, but recurrence is frequent.[7] Patients who relapse can be treated with the same regimen. Stem cell transplant can be pursued in relapsed and refractory settings but carries high treatment-related mortality.[7]

Conclusion

Our case will be a useful addition to the literature of rare cases with isolated cutaneous relapse in patients with a history of follicular lymphoma. We aim to alert the physicians and hematologists about an unusual cutaneous relapse of follicular lymphoma. They can have variable presentation ranging from rapidly growing nodules (which is more common) to subtle induration as in our patient. We suggest that cutaneous lesions in the patient with a history of lymphoma should be thoroughly investigated as they may be the only site of recurrence of the disease.

Table 1. Cases of Follicular Lymphoma Progression with Cutaneous Disease.

Case	Time period for cutaneous presentation after initial diagnosis	Age	Gender	Clinical lesion	Treatment	Outcome
Dhadlie and Strekozov[3]	8 years	70	Female	Sebaceous cyst like lesion on cheek	Systemic therapy (not clear)	Not clear
Talebi-Liasi and Sandhu[4]	3 years	62	Female	Ill-defined erythematous reticular patch with blanchable telangiectasias on scalp	Rituxan	Regressed after 4 cycles but new lesion appeared on cheek 3 months later
Rashid Dar et al[8]	17 years	57	Male	Nodular lesion on right temple of the scalp	RT	Complete remission
	20 years	60		Multiple maculo-nodular of follicular-diffuse spots on the back of chest and shoulders	Tomography	Complete remission
Lopez Aventin et al[9]	17 years	81	Female	Small, clustered, inconspicuous, slightly erythematous papules on the inner aspect of her left thigh	Not reported	Unknown
Ferrer et al[10]	5 years	60	Female	Multiple cutaneous nodules in the legs	Rituxan 4 cycles	Complete remission at 24 months follow-up

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Verbal Informed consent was obtained from the patient for their anonymized information including facial images to be published in this article.

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