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Secondary cutaneous marginal zone B-cell lymphoma presenting as lipoatrophy in a patient with hepatitis C

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Abstract

Background: Hepatitis C viral infection is a significant public health problem; 170 million persons are infected worldwide and the prevalence in the southern part of the United States exceeds two percent. Extrahepatic manifestations of hepatitis C viral infection are common; notably, 15-20% of patients will develop cutaneous manifestations of their disease. There are numerous dermatologic diseases associated with hepatitis C infection, including lichen planus, leukocytoclasticvasculitis, and porphyria cutaneatarda.

Main observation: Recently, epidemiological studies have also demonstrated an association between hepatitis C infection and the development of non-Hodgkin lymphoma, especially marginal zone B-cell lymphoma. Herein we report the unusual case of a systemic marginal zone lymphoma in a patient with hepatitis C infection presenting clinically as localized lipoatrophy.

Conclusion: Lipoatrophy can be a rare and diagnostically challenging presentation of secondary cutaneous marginal zone B-cell lymphoma. The importance of early recognition and detection cannot be over emphasized, as new and effective anti-viral treatments can lead to lymphoma regression in up to 75% of patients. To our knowledge, this is the first case of hepatitis C viral infection associated marginal zone lymphoma to present as localized lipoatrophy. (*J Dermatol Case Rep*. 2014; 8(2): 46-49)

Introduction

Hepatitis C viral (HCV) infection is a significant public health problem; 170 million persons are infected worldwide and the prevalence in the southern part of the United States exceeds two percent of the population.[1] Extrahepatic manifestations are common and fifteen to twenty percent of patients with HCV will develop cutaneous manifestations of their disease.[2] The association of HCV infection with lichen planus, leukocytoclasticvasculitis, and porphyria cutaneatarda are well established; however, recent epidemiological studies have demonstrated a possible association between HCV infection and the development of non-Hodgkin lymphoma (NHL), especially in endemic regions, such as Italy, Japan and southern regions of the United States.[1]

The most commonly reported subtypes of NHL in patients with HCV infection arediffuse large B-cell lymphoma, as well as the more indolent marginal zone B-cell lymphoma (MZL). Twenty to thirty percent of patients with MZL have co-existent HCV infection, compared to two percent of the general population.[1] Multiple small studies have also demonstrated a female predilection for MZL associated with concurrent HCV infection.[3,4]

Cutaneous MZL characteristically presents as red-violaceous papules, plaques or nodules on the trunk and extremities.[5] Herein, we report the unusual case of secondary marginal zone lymphoma (SCMZL) in a patient with HCV infection presenting with localized lipoatrophy, a rather rare manifestation of a cutaneous lymphoma.

Case report

A 61-year-old woman presented with a one-year history of skin dimpling involving the lateral right buttock that was intermittently painful. The patient denied a prior history of trauma or injections to the site. Review of systems was pertinent for a four-year history of night sweats. Her medical history was significant for hypertension, gastroesophageal reflux disease, hypothyroidism, and HCV infection previously complicated by cryoglobulinemia and leukocytoclasticvasculitis.

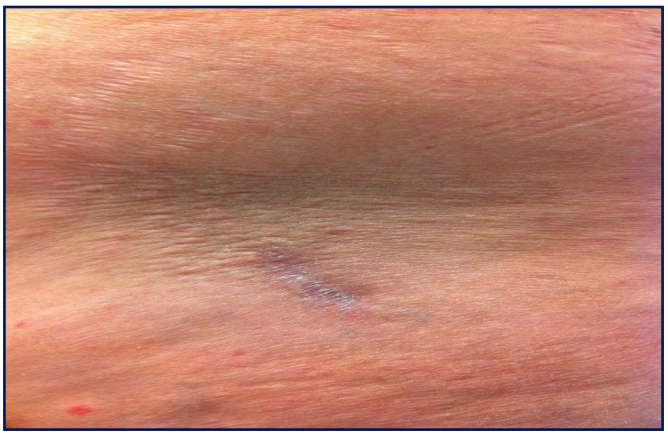

Figure 1

4 x 4 centimeter depressed plaque with accentuation of skin contours on the right lateral buttock.

On physical exam, she was found to have a 4 x 4 centimeter depressed plaque with associated epidermal atrophy and accentuation of skin contours on the right lateral buttock (Fig. 1). Pertinent laboratory findings included leukopenia of 1.3 103/mm^3 (1.7-8.4 103/mm^3), anemia , hemoglobin of 9.3 g/dL (12-16 g/dL) and elevated serum lactate dehydrogenase,416 U/L (84-246 U/L).

Histopathology of the excisional biopsy revealed a lymphohistiocytic infiltrate, scattered plasma cells and occasional large, pleomorphic lymphocytes with prominent nucleoli (Fig. 2A-C). Subsequent immunostaining revealed a nodular to focally diffuse atypical lymphoid infiltrate extending into the subcutaneous fat. The cells were predominately CD20+ B-cells admixed with CD3+ T-cells (Fig. 2D). Scattered large CD30+ cells were noted, as well as nodular aggregates of atypical CD20+ B-cells associated with occasional reactive CD3+, CD5+ and CD43+ T-cells were present. Further testing revealed rare atypical cells that expressed bcl-6, but not bcl-2. A CD23 stain highlighted the follicular dendritic network; both CD30 and cyclin D1 stains were negative. *In situ* hybridization studies for kappa and lambda were negative for light chain restriction. Polymerase chain reaction for immunoglobulin heavy chains was found to be monoclonal. Overall, these histological findings were consistent with MZL.

A positron emission tomography (PET) scan revealed innumerable hypermetabolic soft tissue lesions involving the flank,

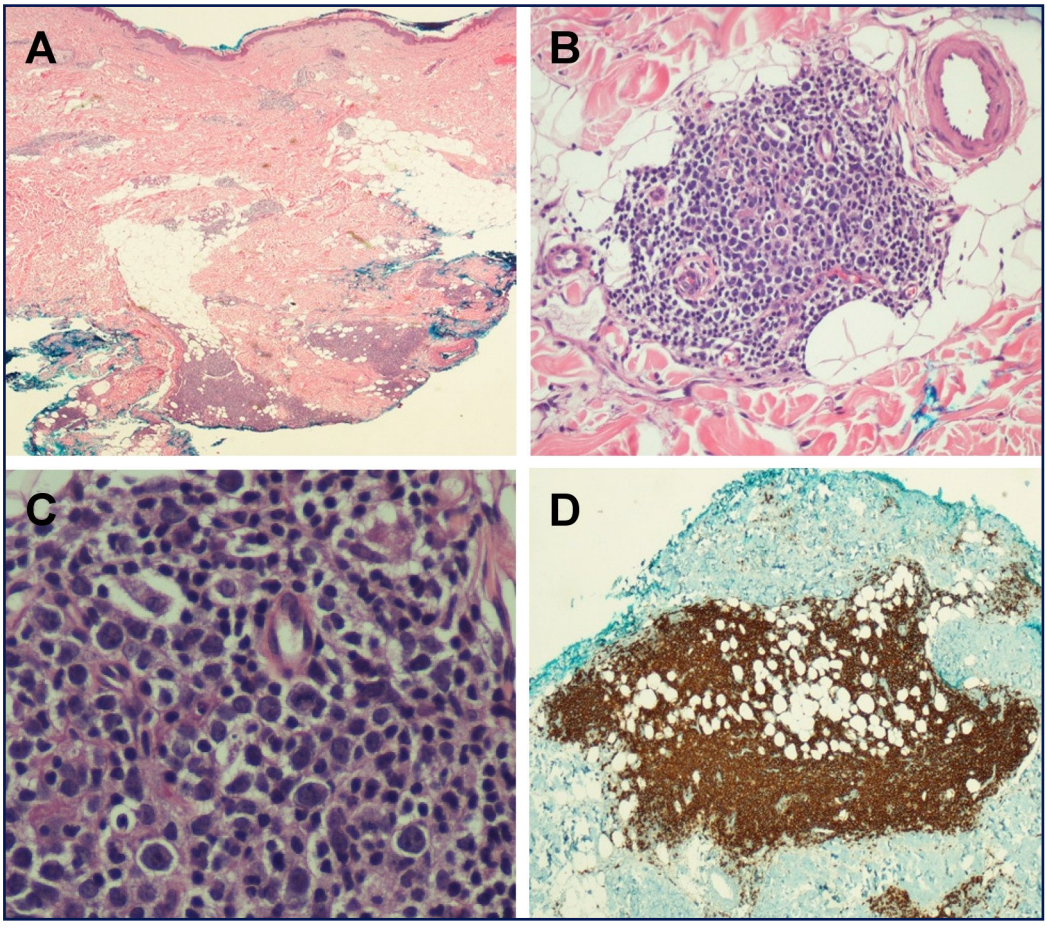

Figure 2

(A-C) Histopathology revealing a lymphohistiocytic infiltrate, scattered plasma cells and occasional large, pleomorphic lymphocytes with prominent nucleoli.

(D) Immunostaining revealing a nodular to focally diffuse atypical lymphoid infiltrate extending into the subcutaneous fat which is predominately CD20+ B-cells admixed with CD3+ T-cells.

lower abdomen/pelvis and thigh, metabolically active lymph nodes in the axilla and pelvis, as well as a small metabolically active nodule in the right posterior parotid gland, all of which likely reflected additional areas of lymphomatous involvement. A computed tomography (CT) scan demonstrated small mediastinal lymph nodes (the largest measuring 1.5 cm in diameter), slightly enlarged para-aortic lymph nodes, splenomegaly and numerous soft tissue nodules. Based on the constellation of findings, a diagnosis of SCMZL was made. The patient was treated with pegylated interferon (90 micrograms weekly), ribavirin (40 mg daily) and boceprevir (200 mg daily). A follow up CT scan six months after initiation of treatment revealed complete resolution of thoracic, abdominal, pelvic or inguinal adenopathy and near complete interval resolution of multiple subcutaneous soft tissue nodules. Given the excellent response of her SCMZL since initiation of HCV treatment and her otherwise indolent presentation, a bone marrow biopsy was not performed and the patient was maintained on the above regimen with close supervision by the Oncology and Infectious Diseases departments without any immediate plans to initiate chemotherapy.

Approximately one year after treatment initiation, laboratory workup revealed improvement of her leukopenia (3.2 x 103/mm^3) and a decrease in serum LDH (252 U/L). The patient also had an improvement in her anemia (13.2 g/dL); however she had received epoetin alpha several months prior. Additionally, the serum HCV RNA was no longer detectable, leading to subsequent discontinuation of the boceprevir. The patient is maintained on ribavirin and pegylated interferon. The patient was lost to dermatology follow up.

Discussion

Numerous investigators have implicated the chronic antigenic stimulation of various infectious agents in the pathogenesis of multiple subtypes of lymphoma, including mucosa-associated lymphoid tissue lymphoma, Burkitt's lymphoma, and sinosal NK/T-cell lymphoma. Similar to the well-documented progression of extra-nodal MZL of the mucosa-associated lymphoid tissue secondary to infection with Helicobacter pylori, antigenic stimulation by HCV and subsequent B-cell proliferation could be related to the development of NHL in this subgroup of patients.[3] Perhaps the strongest evidence for an associative role of HCV in the pathogenesis of NHL comes from a recent report demonstrating demonstrating a lymphoma regression rate approaching 75% after treatment with interferon and ribavirin, with nearly complete regression as was noted in our patient.[1] In another study, Hermine *et al* reported a hematologic response with interferon alpha monotherapyin seven out of nine patients with co-existent HCV and MZL. The other two patients in this study were reported to have either a complete or partial hematologic response to ribavirin.[6] Furthermore, a small multi-center study in Italy conducted by Mazzarro *et al* showed that hematologic response correlated highly with decreased viral load in a cohort of 13 patients with low grade B-cell lymphoma and co-existent HCV treated with pegylated interferon and ribavirin.[7] Although the association between HCV infection and NHL progression is not clearly understood, these recent reports have led some to speculate that HCV may be involved in the pathogenesis of NHL.

Distinguishing primary cutaneous marginal zone B-cell lymphoma from SCMZL is critical both for prognosis, as well as therapeutic approach, as extracutaneous involvement is exceedingly rare in primary cutaneous marginal zone B-cell lymphoma. However, difficulty often arises in distinguishing the two. Clinically, an older age at onset and lesions favoring the head and neck are suggestive of SCMZL.[8] Although one report suggests primary cutaneous marginal zone B-cell lymphoma is more likely to have histologic evidence of epidermal and dermal involvement, as compared to SCMZL which has a greater predilection for the subcutis,[8] the two processes are often histologically indistinguishable and a thorough work-up for systemic involvement, including complete blood examination, peripheral blood flow cytometry, as well as CT and PET scan of the chest, abdomen and pelvisare warranted in all patients to rule out extracutaneous involvement.[5] Early stage SCMZL is traditionally managed conservatively with radiotherapy or alkylating agents. Newer modalities include antimicrobials, ribavirin and interferon in patients with indolent MZL associated with chronic HCV infection[9] and immunotherapy agents targeted against CD20. For example, intralesional rituximab has been shown to be a well-tolerated and effective treatment for Primary cutaneous marginal zone B-cell lymphoma.[10]

To our knowledge, this is the first reportof SCMZL presenting solely with localized lipoatrophy. A case of SCMZL presenting with generalized lipoatrophy has been reported in which an 81-year-old woman who presented with numerous atrophic plaques on her trunk and proximal extremities.[11] Peripheral T-cell lymphoma has also been reported to occur with facial lipoatrophy, but cutaneous nodules had also accompanied this presentation.[12] Additionally, lipoatrophy can occur in the setting of subcutaneous panniculitis-like T-cell lymphoma. However, this occurs after the disappearance of preceding skin lesions, presumably as a consequence of a consumptive panniculitis.[13]

Since lipoatrophy can be a rare and diagnostically challenging presentation of SCMZL, we strongly recommend biopsy and further evaluation of any patient who presents with concurrent HCV infection and lipoatrophy. Although it is possible that the association between HCV infection and SCMZL in our patient may have indeed been coincidental, the importance of early recognition and detection cannot be over emphasized, since treatment of the underlying HCV infection with anti-viral therapy has been shown to lead to the regression of SCMZL in the vast majority of patients.[1]

References

1. Arcaini L, Merli M, Volpetti S, Rattotti S, Gotti M, Zaja F. Indolent B-cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. *Clin Dev Immunol*. 2012; 2012: 638185. PMID: 22956970.
2. Sterling RK, Bralow S. Extrahepatic manifestations of hepatitis C virus. *Curr Gastroenterol Rep*. 2006; 8: 53-59. PMID: 16510035.

3. Paulli M, Arcaini L, Lucioni M, Boveri E, Capello D, Passamonti F, Merli M, Rattotti S, Rossi D, Riboni R, Berti E, Magrini U, Bruno R, Gaidano G, Lazzarino M. Subcutaneous 'lipoma-like' B-cell lymphoma associated with HCV infection: a new presentation of primary extranodal marginal zone B-cell lymphoma of MALT. *Ann Oncol*. 2010; 21: 1189-1195. PMID: 19858084.

4. Arcaini L, Burcheri S, Rossi A, Paulli M, Bruno R, Passamonti F, Brusamolino E, Molteni A, Pulsoni A, Cox MC, Orsucci L, Fabbri A, Frezzato M, Voso MT, Zaja F, Montanari F, Merli M, Pascutto C, Morra E, Cortelazzo S, Lazzarino M.. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. *Ann Oncol*. 2007; 18: 346-350. PMID: 17071937.

5. Bolognia, JL, Jorizzo, JL, Schaffer, JV. Dermatology (2012). 3rd Ed. Section 18. Chapter 119: B-cell lymphomas of the skin.

6. Hermine O, Lefrère F, Bronowicki JP, Mariette X, Jondeau K, Eclache-Saudreau V, Delmas B, Valensi F, Cacoub P, Brechot C, Varet B, Troussard X. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med*. 2002; 347: 89-94. PMID: 12110736.

7. Mazzaro C, Franzin F, Tulissi P, Pussini E, Crovatto M, Carniello GS, Efremov DG, Burrone O, Santini G, Pozzato G. Regression of monoclonal B-cell expansion in patients affected by mixed cryoglobulinemia responsive to alpha-interferon therapy. *Cancer*. 1996; 77: 2604-2613. PMID: 8640712.

8. Gerami P, Wickless SC, Querfeld C, Rosen ST, Kuzel TM, Guitart J. Cutaneous involvement with marginal zone lymphoma. *J Am Acad Dermatol*. 2010; 63: 142-145. PMID: 20462658.

9. Ferreri AJ, Zucca E. Marginal-zone lymphoma. *Crit Rev Oncol Hematol*. 2007; 63: 245-256. PMID: 17583528.

10. Peñate Y, Hernández-Machín B, Pérez-Méndez LI, Santiago F, Rosales B, Servitje O, Estrach T, Fernández-Guarino M, Calzado L, Acebo E, Gallardo F, Salar A, Izu R, Ortiz-Romero PL, Pujol RM, Fernández-de-Misa R. Intralesional rituximab in the treatment of indolent primary cutaneous B-cell lymphomas: an epidemiological observational multicentre study. The Spanish Working Group on Cutaneous Lymphoma. *Br J Dermatol*. 2012; 167: 174-179. PMID: 22356294.

11. Itoh S, Okada N, Wakasa T, Tsudo M, Shintaku M, Kimura T, Horiguchi Y. A case of cutaneous B-cell lymphoma showing multiple lipoatrophy-like skin depressions. *Int J Dermatol*. 2010; 49: 339-341. PMID: 20465679.

12. Yiannias JA, DiCaudo DJ, Maskin E. Peripheral T-cell lymphoma presenting as lipoatrophy and nodules. *Int J Dermatol*. 2006; 45: 1415-1419. PMID: 17184242.

13. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C, Canninga-van Dijk MR, Carlotti A, Geerts ML, Hahtola S, Hummel M, Jeskanen L, Kempf W, Massone C, Ortiz-Romero PL, Paulli M, Petrella T, Ranki A, Peralto JL, Robson A, Senff NJ, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group study of 83 cases. *Blood*. 2008; 111: 838-845. PMID: 17934071.