Unusual case of B cell lymphoma after immunosuppressive treatment for psoriasis

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Abstract

Lymphomas may be induced by the systemic immunosuppressive therapies used to treat psoriasis, such as ciclosporin, methotrexate and tumour necrosis factor (TNF)-α blockers. The biologic agents currently used in psoriasis include alefacept, efalizumab, and the TNF-α antagonists etanercept, infliximab, and adalimumab. Infections and cancer are the main possible consequences of intended or unexpected immunosuppression. We report a 59-year-old man with a history of severe psoriasis vulgaris treated with traditional immunosuppressant drugs followed by anti-TNF-α therapy; the patient was firstly hospitalized for an acute cholestatic toxic hepatitis, which we supposed to be related to adalimumab. The correct diagnosis of T cell/histiocyte-rich large B cell lymphoma (T/HRBCL) was only reached through a gastric biopsy and a second liver biopsy. T/HRBCL is an uncommon morphologic variant of diffuse large B-cell lymphoma not described until now in psoriatic patients receiving immunosuppressive biologic agents. In psoriatic patients, treated with biologic immunosuppressive agents, the suspect of abdominal lymphoma should always be included as differential diagnosis. Abdominal ultrasound evaluation need therefore to be included in the pre-treatment screening as in the follow-up surveillance.

Key words: Psoriasis; Tumor necrosis factor-α blocker; Immunosuppressant; Diffuse large B-cell lymphoma; Lymphoma

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Core tip: We report a case of a rare T cell/histiocyte-rich
large B cell lymphoma localized to liver, gastro-intestinal tract and spleen in a patient with psoriasis treated with traditional immunosuppressant drugs followed by anti-tumor necrosis factor-α therapy. Liver and spleen involvement mimicked at the beginning an inflammatory disease causing a delayed diagnosis of malignancy. We think that abdominal ultrasound evaluation need to be included in the pre-treatment screening as in the follow-up surveillance in psoriatic patients treated with biologic immunosuppressive agents.

INTRODUCTION
Psoriasis is a common chronic inflammatory disease of the skin and joints, which affects approximately 1%-2% of the population. It has been shown that patients with psoriasis are at higher risk of developing malignancies and this risk is greater for patients with severe disease[1,2]. The oncogenic risk is partly related to the immunologic nature of psoriasis and partly to the multiple immunosuppressants used for its treatment. Experimental evidence suggests a primarily T lymphocyte-based immunopathogenesis, with excessive Th1 and Th17 lymphocyte activity in psoriatic lesions. Chronic antigenic stimulation in psoriasis may lead, after a variable period of time, to a dominant clone in the skin and possible evolution towards a cutaneous T-cell lymphoma (CTCL) [3].

Nowadays multiple therapeutic options are available for the treatment of moderate to severe psoriasis. The process of choosing among potential treatment options requires the necessity to weigh the benefits of individual modalities of therapy against their potential risks. Systemic immunosuppressive therapies used to treat psoriasis, such as methotrexate (MTX), cyclosporine (CsA) and mycophenolate mofetil have been associated with an increased risk of lymphoma during treatment, demonstrated in clinical trials involving patients with rheumatoid arthritis and documented in case reports concerning psoriasis patients [1,4].

Furthermore, over the past several years, biologic therapies targeting T cells (e.g., efalizumab, alefacept) or cytokines such as tumor necrosis factor-α (TNF-α) (e.g., infliximab, etanercept, adalimumab) have been introduced for the treatment of moderate-severe psoriasis with a great clinical impact. However, the potential risk to induce serious infections and lymphomas by biologic agents has recently emerged [4].

We report a case of a rare extranodal diffuse large B cell lymphoma localized to liver, gastro-intestinal tract and spleen in a patient with psoriasis treated with traditional immunosuppressant drugs followed by anti-TNF-α therapy. Liver and spleen involvement mimicked an inflammatory disease causing a delayed diagnosis of the malignancy.

CASE REPORT
In February 2009 a 59-year-old man with a 39 years history of moderate to severe psoriasis vulgaris (involving 20% of the patient body surface and nails), treated in the past with several cycles of CsA and a cycle of MTX with partial improvement, was seen at a dermatological centre at the San Gallicano Dermatologic Institute.

The past medical history was consistent for bilateral degenerative maculopathy diagnosed at the age of 49 and essential hypertension diagnosed at the age of 54.

In March 2009 a treatment with etanercept (50 mg twice weekly for 12 wk, followed by 50 mg weekly) was started and stopped in September 2009 due to the complete clearing of psoriasis.

In December 2009 a new cycle of etanercept (50 mg twice weekly) was started due to a relapse of psoriasis. After 1 mo etanercept therapy was stopped because psoriasis continued to worsen. Therefore in February 2010 a therapy with adalimumab (induction dose of 80 mg) was started.

At this stage liver function tests were completely normal as well as all other routine analyses. Two weeks after starting adalimumab therapy the patient presented to the dermatologic outpatient psoriasis centre complaining of generalized malaise and weakness. At the physical examination a jaundice of the sdera was evident. At this stage adalimumab was stopped and the patient was referred to the National Institute for Infectious Diseases “L. Spallanzani”.

Liver function tests showed a grade III increase of both total bilirubin and liver enzymes. Hepatitis A, B and C and auto-antibodies were all negative.

Notwithstanding adalimumab interruption in the following days liver function values continued to rise together with the worsening of the jaundice and the patient physical condition.

An abdominal ultrasound documented an enlarged stenotic liver; cholelithiasis with no dilation of the bile-ducks and spleen enlargement with several hypoechoic areas. Total body computed tomographic scan revealed multiple enlarged celiac and lumbar-aortic lymph nodes, cholangio-nuclear magnetic resonance confirmed the absence of dilation of the bile-ducks. Total-body bone scan highlighted the presence of a small osteolytic area of uncertain nature at D10 level. Due to the worsened clinical picture (total bilirubin values reaching 20 mg/dL and severe pancytopenia) the patient underwent bone marrow and liver biopsies. The bone histology revealed a hypocellular marrow but no evidence of lymphoma. The liver biopsy showed active disease with severe hepatocellular damage caused by heavy lymphocytes.
infiltrate in portal tracts at the interface (Figure 1A). Bridging necrosis was common and surviving hepatocytes often formed hepatic rosettes. Liver lymphocytes were represented mainly by T lymphocytes (CD3+, CD5+, CD56-) sometimes infiltrating the biliary epithelium and the sinusoid, with distinct nuclei and a narrow rim of cytoplasm (Figure 1B). Immunophenotyping revealed CD20+ B cells (Figure 1C) co-expressing CD43 and B-cell lymphoma 2 (BCL-2). Cells were negative for EBV-LMP1 and CD30. A diagnosis of diffuse large B cell lymphoma was made.

A second liver biopsy was performed, showing a diffuse lymphocytic infiltrate (Figure 2A) composed of predominantly small, mature T lymphocytes (CD3+) (Figure 2B) and histiocytes (CD68+) (Figure 2C) with scattered large neoplastic B lymphocytes, consisting of less than 10% of total cells, containing vesicular nuclei, prominent nuclei and moderate amount of cytoplasm. These neoplastic cells expressed CD20 (Figure 2D), CD43, BCL-6, BCL-2, but not EBV-LMP1, CD10, CD138 or CD23, allowing further characterization of the lymphoma as “T cell/histiocyte-rich large B cell lymphoma”. These findings prompt pathologists to reevaluate with immunohistochemical stain of the previously collected splenic specimens, revealing focal scattered large neoplastic lymphocytes in the red pulp, highlighted by CD20 stain (Figure 3). Sarcoid granulomas composed of clusters of epithelioid histiocytes with proliferating lymphocytes hided the neoplastic cells causing the first misdiagnosis.

The described lymphoma was assigned, according to the Ann Arbor Staging System, at group 4 with gastric, splenic, hepatic, abdominal lymph node and vertebral (dorsal column) localizations. The patient immediately started systemic chemotherapy.

Six cycles of CHOP-R have been administered until now with clinical remission and reduction of cholestasis.

DISCUSSION

All patients with psoriasis faced an increased risk of lymphoma with higher relative risks for Hodgkin’s lymphoma and CTCL[5].

In addition to skin cancer, the incidence of lymphoma in those patients employing PUVA therapy in combination with MTX for at least 36 mo was more than 7 times higher than that of cohort members earlier in the study who had less exposure to MTX[6].

A higher incidence of lymphoma with the use of the two monoclonal antibody agents (adalimumab and infliximab) than with the soluble-receptor agent
T-cell/histiocyte-rich B-cell lymphoma (T/HRBCL) is an uncommon morphologic variant of diffuse large B-cell lymphoma, accounting for about 40% of all NHL. T/HRBCL has not been described until now in psoriatic patients receiving immunosuppressive biologic agents. Pathologically, it is distinguished by < 10% malignant B cells amid a majority population of reactive T lymphocytes and histiocytes. The large amount of surrounding inflammatory T lymphocytes may mask the lymphomatous cells, mimicking an hepatitis, or sarcoid like granulomas in the spleen. Accurate diagnosis therefore rests on careful immunohistochemical analysis of the tumour cells and the inflammatory microenvironment.

In our case, the patient was firstly hospitalized for an acute cholestatic toxic hepatitis, that we supposed to be related to adalimumab, and the liver findings were unclear. Our patient underwent splenectomy, but also in this occasion the histology interpretation (performed by...
a different group in another hospital) was misleading. The correct diagnosis was only reached through a gastric biopsy and a second liver biopsy. In psoriatic patients, treated with biologic immunosuppressive agents, the suspect of abdominal lymphoma should always be included as differential diagnosis. Abdominal ultrasound evaluation need therefore to be included in the pre-treatment screening as in the follow-up surveillance.

**COMMENTS**

**Case characteristics**

Two weeks after starting adalimumab therapy the patient presented to the dermatologic outpatient psoriasis centre complaining of generalized malaise and weakness. At the physical examination a jaundice of the sclera was evident.

**Clinical diagnosis**

The worsening of jaundice despite adalimumab interruption excluded liver drug toxicity.

**Differential diagnosis**

The authors considered in the differential diagnosis the following conditions: Intra or extrahepatic cholestatic disorders.

**Laboratory diagnosis**

Liver function tests showed a grade III increase of both total bilirubin and liver enzymes. Hepatitis A, B and C and auto-antibodies were all negative.

**Imaging diagnosis**

An abdominal ultrasound documented an enlarged steatotic liver, cholelithiasis with no dilatation of the bile-ducts and spleen enlargement with several hypoechoic areas. Total body computed tomographic scan revealed multiple enlarged celiac and lumbar-aortic lymph nodes, cholangio-nuclear magnetic resonance confirmed the absence of dilatation of the bile-ducts.

**Pathological diagnosis**

The second liver biopsy performed, showed a diffuse lymphocytic infiltrate composed of predominantly small, mature T lymphocytes (CD3⁺) and histiocytes (CD68⁺) with scattered large neoplastic B lymphocytes, consisting of less than 10% of total cells, containing vesicular nuclei, prominent nucleoli and moderate amount of cytoplasm. These neoplastic cells expressed CD20, CD43, C3 (C63-8) and CD8 and CD23, allowing further characterization of the lymphoma as ‘T cell/histiocyte-rich large B cell lymphoma’.

**Treatment**

The patient immediately started systemic chemotherapy. Six cycles of CHOP-R have been administered until now with clinical remission and reduction of cholestasis.

**Related reports**

T-cell/histiocyte-rich B-cell lymphoma (T/HRLBCL) is an uncommon morphologic variant of diffuse large B-cell lymphoma (DLBCL), accounting for about 40% of all non-Hodgkin lymphomas (NHL). T/HRLBCL has not been described until now as a variant of diffuse large B-cell lymphoma (DLBCL), accounting for about 40% of all NHL.

**Experiences and lessons**

In this case, the patient was firstly hospitalized for an acute cholestatic toxic hepatitis, that the authors supposed to be related to adalimumab, and the liver findings were unclear. The patient underwent splenectomy, but also in this occasion the histology interpretation (performed by a different group in another hospital) was misleading. The correct diagnosis was only reached through a gastric biopsy and a second liver biopsy. In psoriatic patients, treated with biologic immunosuppressive agents, the suspect of abdominal lymphoma should always be included as differential diagnosis. Abdominal ultrasound evaluation need therefore to be included in the pre-treatment screening as in the follow-up surveillance.

**Peer-review**

Useful for the scientific community that uses the immunosuppressive drugs.

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