

## Gastric Mucosa-Associated Lymphoid Tissue Lymphoma in a Patient With Severe Psoriasis Receiving Ustekinumab<sup>☆</sup>



### Linfoma gástrico de tejido linfoide asociado a mucosa en un paciente con psoriasis grave en tratamiento con ustekinumab

To the Editor:

Ustekinumab is a human monoclonal antibody directed against interleukins (IL) 12 and 23, which are involved in the control of infections and tumors and the pathogenesis of psoriasis. Animal model studies have shown that inhibition of IL-12 and IL-23 might promote carcinogenesis.<sup>1</sup>

Biologic therapies are considered to be both safe and well tolerated, but there is concern about their carcinogenic potential. There have been several reports of lymphoproliferative disorders developing in patients under treatment with tumor necrosis factor (TNF) inhibitors.<sup>2-4</sup> We present the case of a 68-year-old man with a history of hypertension, type 2 diabetes mellitus, hypertriglyceridemia, overweight, and ischemic heart disease diagnosed with plaque psoriasis 13 years earlier. Given the severity of his psoriasis, the patient was administered psoralen plus UV-A therapy and methotrexate 15 mg/wk for a year; the treatment showed moderate effectiveness, and rapid recurrence was observed following discontinuation of treatment. In May 2008, the patient was started on concomitant efalizumab and methotrexate (7.5 mg/wk) therapy, which was continued with satisfactory results until efalizumab was withdrawn from the market in 2009. In March 2010, the patient experienced a relapse and was administered ustekinumab, which achieved adequate control of his psoriasis.

In November 2012, the patient was seen at the emergency department of our hospital with complaints of melena and upper abdominal pain. A gastroscopy revealed a gastric tumor with signs of malignancy. The tumor, however, was studied and monitored at another hospital "resultando infructuoso el intento de recuperar las muestras histológicas". The results showed a dense infiltrate composed of atypical lymphocytes without identifiable clusters of nodes. In the immunohistochemical study, the cells were positive for CD20 and BCL2, and negative for CD10, CD30, cyclin D1, and CD5. The use of appropriate histological stains did not identify *Helicobacter pylori* or other microorganisms. A diagnosis of low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma was established, with no metastases identified by positron electron tomography/computed tomography. The patient underwent 19 sessions of radiation therapy, which resulted in complete remission according

to a report dated April 2013, which is when he came for a follow-up visit at our hospital. On examination of this and other reports on the tumor, it was decided to discontinue treatment with ustekinumab. The patient's psoriasis, however, was kept under control with topical treatment, which resulted in almost complete whitening of the lesions. Nevertheless, in August 2013, the patient died suddenly of cerebral infarction.

The risk of malignancy in patients with psoriasis is a hotly debated topic. Some authors have postulated that the risk might be higher than in the general population, even in the absence of treatment, due to the underlying chronic inflammation associated with psoriasis, particularly in patients with comorbidities.<sup>5</sup>

There is also controversy surrounding the risk of lymphomas in patients with psoriasis. It has been postulated that this potentially increased risk might be related to both the pathophysiology of psoriasis and the use of immunosuppressant therapy in this setting.<sup>6</sup>

There have been isolated reports of lymphomas developing in patients treated with a biologic,<sup>3</sup> and even of regression following withdrawal of the drug, pointing to a possible causal relationship.<sup>4</sup>

The development of lymphomas in patients treated with ustekinumab is rare. Data from landmark trials and a recent study of the safety of ustekinumab in psoriasis over a 5-year follow-up period showed that the risk of malignancy per 9000 patient-years was similar to that seen in the general population, with just 1 patient presenting a possible Hodgkin lymphoma.<sup>7</sup>

In our review of the literature, we found just 2 cases of MALT lymphoma that developed during infliximab therapy.<sup>8,9</sup> Both patients had *H pylori* infection. Lymphoma remission was observed in the 2 cases following interruption of the biologic and administration of *H pylori* eradication therapy (Table 1). The authors of both reports speculated that the TNF inhibitor might have acted by promoting *H pylori* infection and/or by directly inducing the lymphoproliferative process. They also did not rule out that previous immunosuppressant therapy or the patients' underlying diseases may have had a carcinogenic role.

MALT lymphoma is a B-cell non-Hodgkin lymphoma. It is usually low-grade and located in the gastrointestinal tract. Ninety percent of patients with gastric MALT lymphoma have concomitant *H pylori* infection. *H pylori* eradication therapy achieves remission in 80% of low-grade lymphomas and in just 50% of high-grade lymphomas. This remission is maintained for many years following the eradication of infection. Recurrence, however, is observed in 10% of cases, hence the need for lifetime endoscopic follow-up. Radiation therapy is the next best option for patients who do not respond to eradication therapy.<sup>10</sup>

In conclusion, we have presented the third case of a patient who developed gastric MALT lymphoma during biologic therapy and the first case involving a patient treated with ustekinumab.<sup>8,9</sup> We cannot, however, rule out that the lymphoma may have been triggered by the patient's chronic inflammatory state induced by psoriasis, or by previous use of immunosuppressant therapy. It is, of course, also possible that the association was merely coincidental. We stress the importance of treatment discontinuation in patients like ours who develop a lymphoma during biologic therapy.

<sup>☆</sup> Please cite this article as: González-Ramos J, Alonso-Pacheco M, Mayor-Ibarguren A, Herranz-Pinto P. Linfoma gástrico de tejido linfoide asociado a mucosa en un paciente con psoriasis grave en tratamiento con ustekinumab. *Actas Dermosifiliogr*. 2015;106:326-327.

**Table 1** Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma in Patients Receiving Biologic Therapy.

Reference	Sex/Age, y	Disease	Previous IS Therapy	Current Treatment	Latency, mo	MALT Lymphoma	Management	Response, mo
Thonhofer et al. <sup>8</sup>	F/64	RA	Methotrexate Sulfasalazine	Infliximab Methotrexate	21	Paranasal sinus	Interruption of infliximab and methotrexate Eradication <i>Hp</i> therapy	Complete, 3
Girard et al. <sup>9</sup>	M/50	Psoriasis	PUVA Ciclosporin Methotrexate Etanercept Efalizumab	Infliximab	13	Stomach	Interruption of infliximab Eradication <i>Hp</i> therapy Methotrexate (psoriasis)	Partial, 1
Current case	M/68	Psoriasis	PUVA Methotrexate Efalizumab	Ustekinumab	32	Stomach	Radition therapy Interruption of ustekinumab	Complete, 4

Abbreviations: F, female; *Hp*, *Helicobacter pylori*; IS, immunosuppressant; M, male; PUVA, psoralen plus UV-A therapy; RA, rheumatoid arthritis.

## References

- Santos-Juanes J, Coto P, Galache F C. Ustekinumab. Neoplasias y otros aspectos de seguridad. *Actas Dermosifilogr.* 2012;103 Suppl 3:39–44.
- Gordon KB, Papp KA, Langley RG, Ho V, Kimball AB, Guzzo C, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (Part II of II): Results from analyses of infections and malignancy from pooled phase II and II clinical trials. *J Am Acad Dermatol.* 2012;66:742–51.
- Raval G, Mehta P. TNF-alpha inhibitors: Are they carcinogenic. *Drug Healthc Patient Saf.* 2010;2:241–7.
- Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum.* 2002;46:3151–8.
- Daudén E, Castañeda S, Suárez C, García-Campayo J, Blasco AJ, Aguilar MD, et al. Integrated approach to comorbidity in patients with psoriasis. Working group on psoriasis-associated comorbidities. *Actas Dermosifilogr.* 2012;103 Suppl 1: 1–64.
- Gelfand JM, Shin DB, Neimann Al Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. *J Invest Dermatol.* 2006;126:2194–201.
- Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis: Final results from 5 years of follow-up. *Br J Dermatol.* 2013;168:844–54.
- Thonhofer R, Gaugg M, Kriessmayr M, Neumann HJ, Erlacher L. Spontaneous remission of marginal zone B cell lymphoma in a patient with seropositive rheumatoid arthritis after discontinuation of infliximab-methotrexate treatment. *Ann Rheum Dis.* 2005;64:1098–9.
- Girard C, Guillot B, Bessis D. Gastric MALT lymphoma in a patient receiving infliximab for psoriasis. *Br J Dermatol.* 2008;159:497–8.
- Gisbert JP, Calvet X. Review article: Common misconceptions in the management of *Helicobacter pylori*-associated gastric MALT-lymphoma. *Aliment Pharmacol Ther.* 2011;34:1047–62.

J. González-Ramos,\* M.L. Alonso-Pacheco,  
A. Mayor-Ibarguren, P. Herranz-Pinto

*Servicio de Dermatología, Hospital Universitario La Paz, Madrid, Spain*

\*Corresponding author.

E-mail address: [gnzalezramosjessica@gmail.com](mailto:gnzalezramosjessica@gmail.com)  
(J. González-Ramos).

## Phrynoderma After Biliopancreatic Diversion<sup>☆</sup>



### Frinoderma asociado a derivación biliopancreática

Current surgical techniques for the treatment of morbid obesity can lead to major systemic complications. Biliopan-

creatic bypass surgery is a mixed restrictive-malabsorptive type of bariatric surgery that combines partial gastrectomy with a gastroileal anastomosis, causing the bile and pancreatic secretions to mix with the foods only in the final 50 cm of the small bowel. In the long term, this considerably reduces the absorption of vitamins, oligoelements, and essential fatty acids.

Our patient was a man of 46 years of age, with a history of obesity, hypertension, tuberculous lymphadenitis in 2005, a biliopancreatic bypass operation in 1999, and operations for an anal fistula and to perform dermolipectomy in the hypogastrium and flanks. He was on treatment with valsartan, venotonic agents, ferrous sulfate, and Dayamin-

<sup>☆</sup> Please cite this article as: Abad L, Omiste T, Vera J, Gilaberte Y. Frinoderma asociado a derivación biliopancreática. *Actas Dermosifilogr.* 2015;106:327–329.