



# ACTAS Dermo-Sifiliográficas

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## LETTERS TO THE EDITOR

### Comment on: Late-Onset Acquired Generalized Lipodystrophy with Muscle Involvement<sup>☆</sup>

### Comentario a: Lipodistrofia generalizada adquirida de inicio tardío y con afectación muscular

To the Editor:

After reading the interesting case report by Llamas-Velasco et al.,<sup>1</sup> we would like to add a comment.

The authors described a case of acquired generalized lipodystrophy (AGL) with muscle involvement. The index patient with AGL had normal muscle strength and biopsy report. The evidence of muscle involvement were the presence of high creatine kinase levels and a myopathic pattern on electromyography.

Furthermore, the patient had hypothyroidism with dyslipidemia for which she was receiving levothyroxine and fenofibrate. The authors do not mention neither the dose for these 2 drugs nor the effectiveness of the levothyroxine

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supplementation (the results of serum thyroid stimulating hormone level). High serum creatine kinase levels and a myopathic pattern on electromyography have been reported in patients with hypothyroidism and also in such patients when they are receiving hypolipidemic therapy (fenofibrate) even in the absence of clinical evidence of muscular involvement.<sup>2,3</sup>

## References

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### Microsatellite and Genetic Instability in Patients With Muir-Torre Syndrome<sup>☆</sup>

### Estudio de inestabilidad de microsatélites y genético de los pacientes con síndrome de Muir-Torre

To the Editor:

First we wish to congratulate the authors of the case report *Extraocular Sebaceous Carcinoma*, published in volume 103 of *Actas Dermosifiliográficas*.<sup>1</sup> We believe that much can

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be learned from the 2 cases described, which furthermore highlight the role of the dermatologist as the first specialist in a position to detect serious diseases. We have had a similar experience, and wish to describe the molecular and genetic tests that are available for these types of cases.

The patient was 47 years of age and was diagnosed with extraocular sebaceous carcinoma. He was referred for follow-up, during which we detected several sebaceous adenomas and hyperplasias, which were excised because malignancy could not be clinically ruled out. Given that some of these lesions displayed varying degrees of dysplasia, samples were analyzed for microsatellite instability, which was positive, in an initial immunohistochemical screening. Based on these data and faced with a suspected case of Muir-Torre syndrome (MTS), a detailed analysis of family cancer history was conducted. This revealed the presence of several first- and

second-degree relatives who had died from colon and urothelial cancer.

MTS is a highly penetrant autosomal dominant disease, which is either inherited or arises spontaneously. It affects patients who are heterozygous for the causative mutation and shares a common genetic basis with hereditary non-polyposis colon cancer (*hMSH2*).<sup>2</sup> MTS is characterized by the presence of multiple sebaceous gland tumors, including sebaceous hyperplasia, sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma, and various visceral tumors, including colorectal, gastric, esophageal, breast, and genitourinary tumors.<sup>2</sup>

MTS is caused by mutations that affect DNA mismatch repair (MMR) proteins. The MMR proteins most closely associated with MTS are MSH2, MLH1, and MSH6, although PMS2 and MLH3 have also been recently implicated.<sup>2</sup> At our hospital, we perform immunohistochemistry for MSH2, MSH6, MLH1, and PMS2 proteins in all suspected cases of MTS. If these proteins are not expressed, as occurred with our patient, the next step is an analysis of DNA microsatellite instability. In our case a microsatellite instability (MSI) analysis was performed by polymerase chain reaction (PCR) amplification of a panel of 5 markers (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) and 2 control markers (Penta C and Penta D).

PCR was subsequently performed with specific fluorescent primers using MSI Analysis System Version 1.2 (Promega), and fragment analysis was conducted using an ABI Prism 3730 sequencer and the corresponding software. These tests revealed high-level microsatellite instability. Specifically, instability of the following markers was observed: NR-21, BAT-25, BAT-26, and MONO-27. The next stage consisted of automated extraction of DNA from the tumor samples and sequencing of exon 10 of the *MSH2* gene, followed by electrophoresis and sequencing analysis (ABI3730; SeqScape v 2.5). Direct molecular analysis of mutation c.1544.1548delCAGTG of exon 10 of the *MSH2* gene was positive. The sensitivity of this technique is 99.9%. Analysis of a sample of the patient's peripheral blood using the same approach identified the same alteration. Subsequent analyses of the peripheral blood of the patient's immediate relatives (3 siblings and 2 children) were positive for the 1544.1548 mutation of CAGTG in exon 10 of the *MSH2* gene in 1 of the siblings and 1 of the children.

All mutation carriers were included in a screening program for individuals with a high risk of colon adenocarcinoma and urothelial cancer, and female carriers underwent exhaustive gynecological examinations. During the

following 2 years our patient presented multiple colonic tubular adenomas with high-grade dysplasia, and finally underwent a prophylactic subtotal colectomy due to the impossibility of controlling flat adenomas. We detected 2 new sebaceous carcinomas of less than 3 mm in diameter, one on the face and another on the forearm. There was no clinical evidence of malignancy.

Sebaceous carcinoma can appear benign and unremarkable,<sup>3</sup> and can sometimes resemble other lesions. This neoplasm is an adnexal malignant tumor derived from the epithelium of the ocular (meibomian) or extraocular sebaceous glands. It is locally very aggressive and has a strong tendency toward vascular and perineural invasion and local recurrence.<sup>3</sup> Multiple studies indicate that all patients in whom sebaceous neoplasia is detected should undergo testing to rule out internal visceral tumors, and where possible avail of the appropriate molecular and genetic tests.<sup>2</sup>

It is particularly important to identify these individuals, as peripheral blood tests can also detect instability markers, which are important to identify relatives carrying the mutation early in life and prior to the onset of symptoms. The risk of transmitting the mutation is 50% for each child and prenatal diagnosis is possible in these families.

## References

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