Gastroenterología y Hepatología 46 (2023) 645–646

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

LETTER TO THE EDITOR

Hereditary GIST syndrome secondary to germline mutation in *KIT*

Síndrome de GIST hereditario y secundario a una mutación germinal en KIT

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract, characterised by activating somatic mutations in the *KIT* or *PDGFR* genes. The vast majority of GISTs are sporadic, but unusual hereditary forms have been reported.[1]

We present the case of a 62-year-old male patient, born in 1960 with no children, referred for a family history of GIST. His father had died from a diagnosed gastric GIST at age 68, and two of his five siblings had undergone surgery on several occasions for multifocal bowel GISTs (diagnosed at age 50 and 55, respectively). The patient had a history of two skin melanomas resected at age 37 and 53 and was in remission. A genetic study was requested in the two affected siblings and later in the patient, confirming the presence of a pathogenic germline mutation in *KIT* (c.2458G>T, p.Asp280Tyr, exon 17). His other three siblings rejected the genetic study and remain asymptomatic (Fig. 1). In coordination with Oncology, the patient began follow-up with abdominal computed tomography (CT) every three years and annual gastroscopy.

In a screening gastroscopy, with the patient asymptomatic, a submucosal lesion of 4 cm was detected in the antrum with central ulceration suggestive of GIST. An endoscopic ultrasound confirmed the presence of a hyperechogenic subepithelial lesion dependent on the muscle itself with suspicious endosonographic criteria. The biopsies showed positivity for CD117 and DOG1, without mitosis and a Ki67 index of 10%; compatible with GIST, without being able to establish the risk of progression due to the size of the sample. Abdominal CT ruled out distant extension and the patient was referred for surgery. Histological analysis of the surgical specimen confirmed the presence of a low-grade 4 cm GIST (G1), with 4 mitoses/5 mm^2, proliferation index (Ki-67) of 30%, free margins and very low risk of recurrence (1.9%). No lymphovascular, perineural or nodal invasion (T2N0M0) was identified.

GISTs are rare tumours derived from the neoplastic transformation of interstitial cells of Cajal. Most are sporadic and up to 85% have somatic mutations that lead to gain-of-function of the *KIT* or *PDGFR* genes. The remaining 15% are usually associated with mutations in other genes such as *NF1*, *SDH* or *BRAF*.[1] Hereditary GISTs due to germline *KIT* or *PDGFR* mutations are extremely rare, with just over 50 familial cases reported to date.[2] The mutation has autosomal dominant inheritance with high penetrance.[1]

Familial GISTs have an early onset, with a mean age of presentation of 48 years, 10 years lower than that of sporadic cases.[3] Most are multifocal and can affect the entire gastrointestinal tract, which increases the risk of complications such as bleeding or perforation. Very often they are associated with skin pigmentation abnormalities (hyperpigmentation, lentigines or vitiligo), urticaria pigmentosa and alterations in intestinal motility (dysphagia, constipation). Other cancers have been reported in germline carriers of *KIT* variants, although it is unclear whether these cancers are attributable to the underlying genotype.[3,4]

Medical treatment should follow the same guidelines as for sporadic GISTs. However, the multiplicity of tumours usually complicates surgical treatment.[5] The efficacy of imatinib in sporadic GISTs depends on the type of activating mutation and the codon affected, with *KIT* exon 11 mutations being the most common and those that respond best to said drug.[2] Although there is scarce evidence on the role of imatinib in patients with germline mutations, several cases have been described with very favourable responses. In fact, some authors recommend considering indefinite treatment with imatinib in patients with multiple, fast-growing GISTs and/or those larger than 3 cm.[5]

With the increasing availability of genetic testing, the number of families with hereditary GIST is likely to increase. Unfortunately, there are no recommendations on the type and frequency of screening to be performed on these individuals or when to start it. Some authors recommend frequent gastroscopy and CT or abdominal magnetic resonance imaging (MRI) at varying intervals of six months to three years based on findings.[5] Until formal guidelines are available, screening in asymptomatic carriers should be individualised and guided by the underlying genotype and family history.

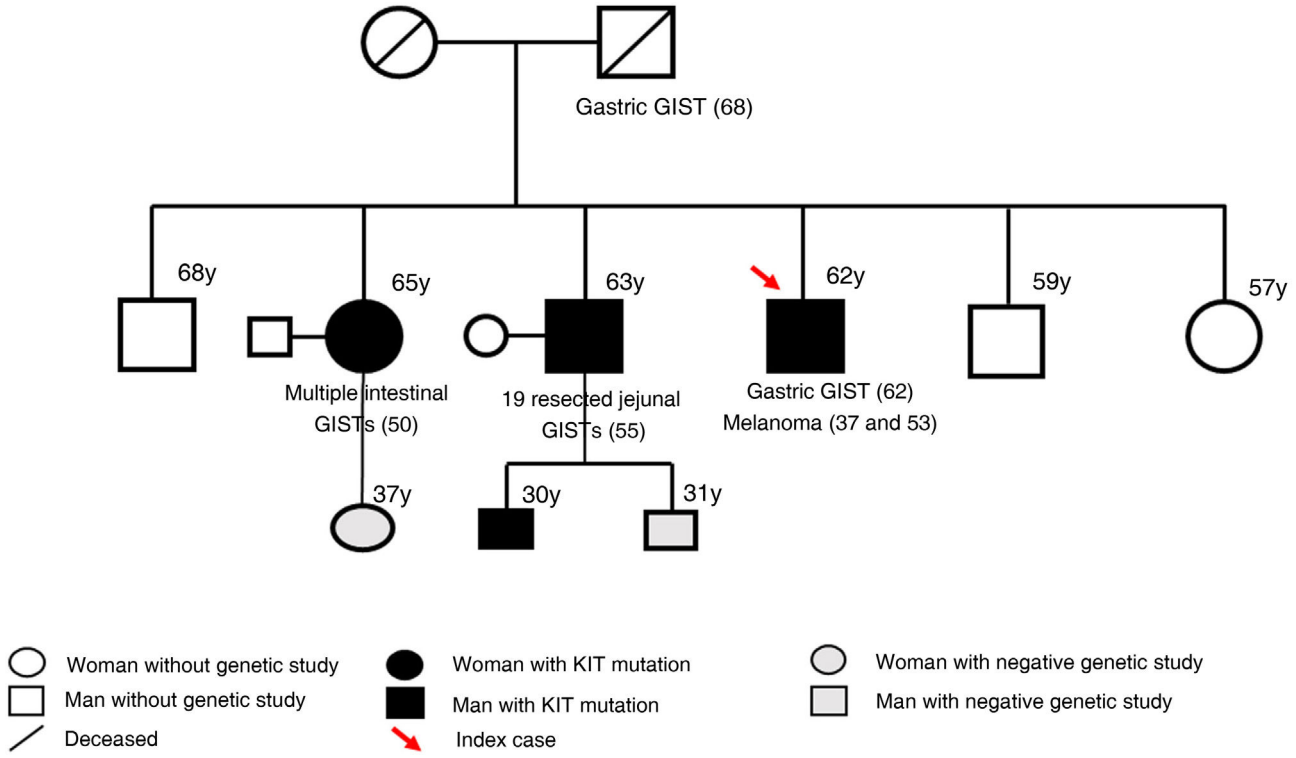

Figure 1 Family tree.

Conflicts of interest

The authors declare they have no conflicts of interest related to this article.

Funding

This study received no specific funding from public, private or non-profit organisations.

Acknowledgements

Author contribution: Eukene Rojo, Pablo Miranda, Raquel Herranz and Felipe de la Morena contributed to the drafting of the article. All authors critically reviewed the content of the manuscript and approved the final version.

References

1. Ricci R. Syndromic gastrointestinal stromal tumors. Hered Cancer Clin Pract. 2016;14:15, http://dx.doi.org/10.1186/s13053-016-0055-4.
2. Brodey A, Kounnis V, Hawkes L, Jones RL, McVeigh TP, Cojocaru E. KIT-associated familial GIST syndrome: response to tyrosine kinase inhibitors and implications for risk management. Oncologist. 2022;27:615–20, http://dx.doi.org/10.1093/oncolo/oyac120.
3. Li FP, Fletcher JA, Heinrich MC, Garber JE, Sallan SE, Curiel-Lewandrowski C, et al. Familial gastrointestinal stromal tumor syndrome: phenotypic and molecular features in a kindred. J Clin Oncol. 2005;23:2735–43, http://dx.doi.org/10.1200/JCO.2005.06.009.
4. Farag S, Van der Kolk LE, van Boven HH, van Akkooi ACJ, Beets GL, Wilmink JW, et al. Remarkable effects of imatinib in a family with young onset gastrointestinal stromal tumors and cutaneous hyperpigmentation associated with a germline KIT-Trp557Arg mutation: case report and literature overview. Fam Cancer. 2018;17:247–53, http://dx.doi.org/10.1007/s10689-017-0024-8.
5. Bachet J-B, Landi B, Laurent-Puig P, Italiano A, Le Cesne A, Levy P, et al. Diagnosis, prognosis and treatment of patients with gastrointestinal stromal tumour (GIST) and germline mutation of KIT exon 13 q. Eur J Cancer. 2013;49:2531–41, http://dx.doi.org/10.1016/j.ejca.2013.04.005.

Eukene Rojo*, Pablo Miranda, Raquel Herranz, Felipe de la Morena

Servicio de Gastroenterología, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP) y Universidad Autónoma de Madrid, Madrid, Spain

* Corresponding author.
E-mail address: eukenerojo@hotmail.es (E. Rojo).