Phacomatosis Pigmentokeratotica:

mosaic RASopathies as a key to better understand cancer

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INTRODUCTION

Phacomatosis pigmentokeratotica (PPK) belongs to the group of mosaic RASopathies, which are emerging as a new class of congenital diseases. While in the past all efforts were dedicated to establishing morphologic and phenotypic categories, today they are focused on understanding the implicated genetics and the molecular pathways that originate these diseases. We report a new case of this rare entity in which a single dominant mutation in a mosaic pattern explains the presence of the different cutaneous manifestations as well as neoplastic ones.

CASE REPORT AND METHODS

17-year-old male presented since birth with a large sebaceous nevus (SN), oral papillomatous hyperplasia (OPH) lesions in the right hemimucosa, a speckled papulous nevus (SLN) with checkerboard pattern and other extracutaneous alterations including cardiac, musculoskeletal, ocular and neurological. Furthermore, the patient developed two primary rhabdomyosarcomas along his lifetime (one at 4 months and the other at 12 years of age). With the clinical diagnosis of Phacomatosis Pigmentokeratotica (PPK), genetic tests were performed in order to determine the existence of a mutation responsible for the appearance of the cutaneous, extracutaneous and tumoral manifestations. DNA was extracted and analyzed by Sanger sequencing from tissue biopsies from SN, several melanocytic lesions within SLN both acquired and congenital, OPH, both rhabdomyosarcomas and also from normal skin and peripheral blood. We found a HRAS c.37G>C mutation which corresponds to a p.Gly13Arg substitution in all of the pathological samples, while skin and blood resulted wild type.

DISCUSSION

PPK is an example of mosaicism, which is characterized by the association of an epidermal nevus and a SLN and extracutaneous manifestations (i.e. neurological, skeletal, cardiac, ocular or metabolic...). Until recently, PPK was considered an epidermal nevus syndrome and the ethiopethogenteical hypothesis of "twin-spotting" was accepted. In 2013, Groesser et al published PPK was caused by a postzygotic mutation in HRAS after studying DNA samples from different affected tissues of 6 PPK patients. They revealed that 4 of them had a c.37G>C and 2 had a c.182A>G mosaic HRAS mutation. However, since that initial description, 5 more PPK cases with available genetic study have been reported, 2 of them showing a BRAF and 1 a KRAS mutation. Anyhow, since those alterations involve the Ras-Raf-MEK-ERK pathways, we can affirm that PPK is a mosaic RASopathy, just as are SN and epidermal keratinocytic nevus or Schimmelpenning syndrome among others. Mutations on these RAS signalization pathways have an outstanding role on tumorigenesis and are present in about 30% of the human cancers. Likewise, a higher incidence of neoplasia has been observed in patients with germline RASopathies, as well as in patients with ENS. Furthermore, a relationship to cancer has also been noticed in PPK, especially urothelial carcinomas and rhabdomyosarcomas, with a recent report of a case of this tumour in a patient with KRAS mutated PPK. Moreover HRAS, NRAS and PIK3Ca mutations have been reported in some sporadic rhabdomyosarcomas¹⁴. Nonetheless, to our knowledge an HRAS c.37G>C substitution has never been related to the appearance of rhabdomyosarcoma neither in case of PPK, nor in sporadic tumours. Furthermore, to our knowledge this is the first case of PPK in which a mutation in HRAS causes rhabdomyosarcoma.

CONCLUSION

It is worth noting that when we come across malignant tumors in children with no family history or patients with multicentric primary cancers, a mosaic oncogenic mutation should be suspected. Cases like this point to consider that cutaneous mosaicisms are just the tip of the iceberg, the visible part of much more complex diseases which might have been so far underdiagnosed. Dermatologist stand on a privileged position to identify patients at risk and coordinate the multidisciplinary team they need.