Atypical hypertrophy of retinal pigment epithelium manifesting as the first sign of familial adenomatous polyposis

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SUMMARY
A female patient in her 20s presented to a routine ophthalmology appointment. Medical history was unremarkable. Family history was notable for gastrointestinal endoscopy revealed 500–1000 colonic adenomatous polyps, with lesions with a maximum size of 25 mm, some flat, with a preferential distal distribution, in the rectum. Pathological evaluation did not reveal any progression to submucosal invasion of the lesions. Genetic testing showed an heterozygotic variant c.3183_3187delACAAA p.(Gln1062*). In the APC gene, classified as pathogenic.

BACKGROUND
Pigmented lesions of the ocular fundus can be detected in routine evaluation, especially with the recently developed widefield and ultra-widefield imaging. Congenital hypertrophy of retinal pigmented epithelium (CHRPE) consists of a proliferation of the cells which constitute this pigmented layer of the retina. Clinical features divide these lesions into typical forms, which occur in 0.5% of the population and are benign and atypical forms, which are associated with familial adenomatous polyposis (FAP) and its variants.

CASE PRESENTATION
A female patient in her 20s presented to a routine ophthalmology evaluation. She had no visual complaints and decided to have an ophthalmology appointment as she could not remember her last observation. Medical history was unremarkable. Family history was noteworthy for a second-degree relative who passed away due to intestinal cancer in her late 60s. Fundus examination revealed bilateral, multiple, flat, oval, pigmented lesions with an irregular halo of atrophy. The patient was diagnosed with atypical congenital hypertrophy of retinal pigmented epithelium. Investigation of extracutaneous associations was performed, including upper and lower endoscopy, which revealed 500–1000 colonic polyps with a maximum size 25 mm. Pathology did not reveal submucosal invasion. Genetic testing detected an adenomatous polyposis coli mutation (heterozygotic variant c.3183_3187delACAAA p.(Gln1062*)).

OUTCOME AND FOLLOW-UP
The patient is currently under follow-up for other gastrointestinal malignancies and extraintestinal tumours which can present in FAP variants including bone cysts, hamartomas, soft tissue tumours (in Gardner’s variant) and central nervous system (CNS) neuroepithelial tumours (in Turcot’s variant). An annual ophthalmology visit (with optic coherence tomography (OCT) capturing the lesions, retinography and FAF) has also been established as part of her follow-up schedule to detect enlargement and progression of ocular lesions. In cases of suspected progression, fluorescein angiography and echography are options to detect developing malignancy.

DISCUSSION
Pigmented lesions of the ocular fundus are not rare. Multiple mechanisms can underlie their development, including infection, inflammation and neoplastic (both congenital and benign or developmental and malignant). In terms of pathophysiology, these lesions may arise from the RPE or melanocytic cells, both contain melanin. In terms of pathophysiology, these lesions may arise from the RPE or choroidal melanocytes, as both contain melanin. Genetic testing showed an heterozygotic variant c.3183_3187delACAAA p.(Gln1062*). In the APC gene, classified as pathogenic.

TREATMENT
Due to her young age, this patient is currently under surveillance by gastroenterology and general surgery in order to determine the best timing for a prophylactic surgical intervention. A prophylactic colectomy is frequently necessary in these patients in order to prevent malignant transformation. In cases of untreated FAP, progression to colonic carcinoma is almost universal.

INVESTIGATIONS
Systemic investigation was performed, and lower gastrointestinal endoscopy revealed 500–1000 colonic adenomatous polyps, with lesions with a maximum size of 25 mm, some flat, with a preferential distal distribution, in the rectum. Pathological evaluation did not reveal any progression to submucosal invasion of the lesions. Genetic testing showed an heterozygotic variant c.3183_3187delACAAA p.(Gln1062*) in the APC gene, classified as pathogenic.

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configuration). Two forms of CHRPE have been described: typical and atypical. The typical form is unilateral in almost all cases and is subdivided clinically into solitary and grouped forms. Solitary forms are 2–5-mm sized, black, flat, round, single lesions with depigmented lacunae within them. Grouped forms are similar but smaller lesions, less than 2 mm in size, resembling ‘bear tracks’. Although no systemic involvement is associated, progression to adenocarcinoma of the RPE from solitary lesions occurs in a minority of cases and surveillance is required.

The atypical form, as presented in this case, differs by being bilateral, multiple and familial. Histology differs as in the atypical form there is RPE hyperplasia and thickening of Bruch’s membrane, while both these layers are normal in the typical form. Systemic associations include familial adenomatous polyposis and its variants, Gardner’s and Turcot’s syndrome. FAP is responsible for less than 1% of colorectal carcinoma. Morphologically, this syndrome correlates with the development of hundreds of adenomas in the colon and rectum. The syndrome is inherited mainly in an autosomal dominant, highly penetrant fashion, caused by a mutation in the APC gene, on chromosome 5q21-22. FAP poses an almost universal lifetime risk of colorectal cancer. There is also a less severe phenotype caused by a mutation in the mutY DNA glycosylase (MUTYH) gene. Surveillance of these patients includes upper and lower gastrointestinal endoscopy every 1–2 years, depending on the type of FAP and presence of adenomas. When a diagnosis of FAP is made, a prophylactic colectomy while the disease is in its premalignant form is very important, and although the timing of surgery is not defined, it is recommended when there are large adenomas or they reveal a high grade of dysplasia, which tends to occur between 15 and 25 years of age. There is pivotal importance to identifying and distinguishing atypical CHRPE lesions as they may alert to the presence of non-diagnosed FAP. Atypical CHRPE is considered the inaugural manifestation of FAP and may be detected in routine ophthalmological examination. As in this case, an early identification of the lesion and referral prevented progression of colonic disease to potentially life-threatening stages.

Learning points

- Congenital hypertrophy of retinal pigmented epithelium (CHRPE) is not an uncommon lesion, and widefield/ultra-widefield imaging may increase its identification.
- Clinical features may help to distinguish atypical forms of CHRPE which may be the first manifestation of familial adenomatous polyposis (FAP).
- Identification and surveillance of FAP patients may be life-saving as progression to malignant colorectal cancer is universal.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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REFERENCES