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Case Report

Ocular Manifestation of Familial Adenomatous Polyposis

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Abstract

Gardner Syndrome is a phenotypic variant of Familial Adenomatous Polyposis (FAP) characterized by extracolonic manifestations including pigmented ocular fundus lesions with malignant polyps in the large intestine. We present the case of a 41-year-old female with FAP, who presented with numerous congenital hypertrophy of the retinal pigment epithelium ocular lesions. We describe the case report along with a literature review of ocular findings in Gardner syndrome.

Keywords: Gardner Syndrome, Familiar Adenomatous Polyposis, Eye

Introduction and Epidemiology

Gardner Syndrome is on the spectrum of Familial Adenomatous Polyposis (FAP), a hereditary cancer syndrome, in which numerous malignant polyps arise along the intestinal lumen of the colon [1]. It is a phenotypic variant of FAP with extracolonic manifestations including characteristic multiple, pigmented ocular fundus lesions [2,3]. In the early 1950s, Dr. Eldon J. Gardner described a hereditary association between intestinal polyposis and various tumors throughout the body from osteomas ('hard tumors") and subcutaneous lesions ("soft tumors") predominantly epidermoid cysts, fibromas and ill-defined masses of connective tissue [4-7]. In 1958, WG Smith termed this constellation of findings "Gardner Syndrome" [8]. The first association of ocular involvement was reported in 1980 with findings of numerous benign fundus lesions, specifically hypertrophy of the retinal pigment epithelium (CHRPE) [9].

The incidence of Gardner Syndrome is between 1 in 8,300 and 1 in 14,025 live births with a uniform worldwide distribution while reports of prevalence are estimated to be between 1:6,850 and 1:31,250 individuals across the world [10-13]. An important limitation of these estimates is that classifications based on extraintestinal manifestations of FAP may be difficult to approximate as syndromes such as Turcot Syndrome (FAP in association with a primary CNS tumor) [14] and Gardner Syndrome appear to be phenotypic variants of FAP that have variable penetrance of causative mutations [2]. There appears to be no racial or gender predilection [10-12].

Pathophysiology

The pathophysiology of Gardner Syndrome and FAP involves various mutations in the *APC, RAS,* and *TP53* genes, deletion of the *DCC* gene, and loss of DNA methylation. These genetic changes culminate in unimpeded progression of the adenoma-to-carcinoma sequence, leading to colonic malignancy [15]. Researchers posit that the specific area of mutation may determine the type and severity of extracolonic manifestations [2,16]. Researchers have found that Gardner syndrome-related retinal lesions are associated with mutations between codons 311 and 1444 of the 5q21-q22 band of the *APC* gene [17-19].

Case Report

A 41-year-old woman status-post prophylactic proctocolectomy with a strong family history of FAP presented for an eye examination, in September 2018, due to gradual intermittent blurry vision in both eyes over the previous few months. She reported no significant previous ocular history. Family history

was significant for a diagnosis of FAP in her mother, son, nephew, two sisters and brother; all three siblings had passed away from colon cancer at the ages of 36, 48 and 51 years of age, respectively. The patient had been diagnosed with FAP following a colonoscopy in October 2015, underwent prophylactic proctocolectomy in 2016, small bowel resection, partial gastrectomy and excision of a mesenteric mass in 2017 and subsequent radiation for a pelvic mass.

On examination in the office, the extraocular movements were intact bilaterally. Pupils were normal in size and reactive. Visual acuity was 20/25 in each eye with full visual fields bilaterally with early presbyopia. Intraocular pressure measurements were within normal range.

Anterior segment examination revealed a large, pigmented conjunctival lesion infero-temporally in the left eye with no other significant findings. Dilated fundus examination revealed clear media with pink and healthy optic nerves bilaterally. Multiple, flat, well-defined, oval, teardrop-shaped subretinal pigmented lesions were noted in multiple quadrants of both eyes (Figures 1-2). No retinal edema or hemorrhage was present.

1a

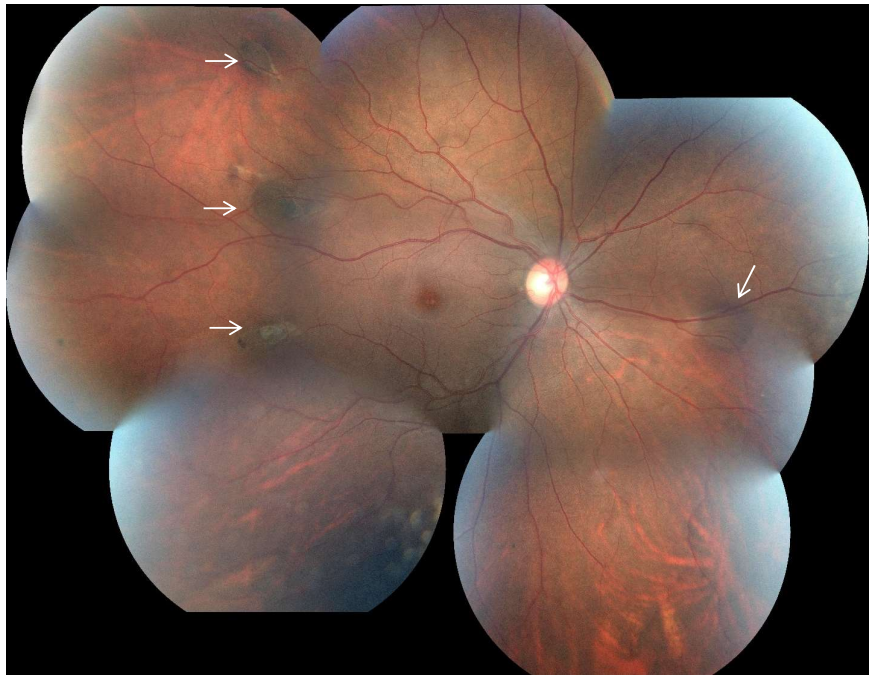
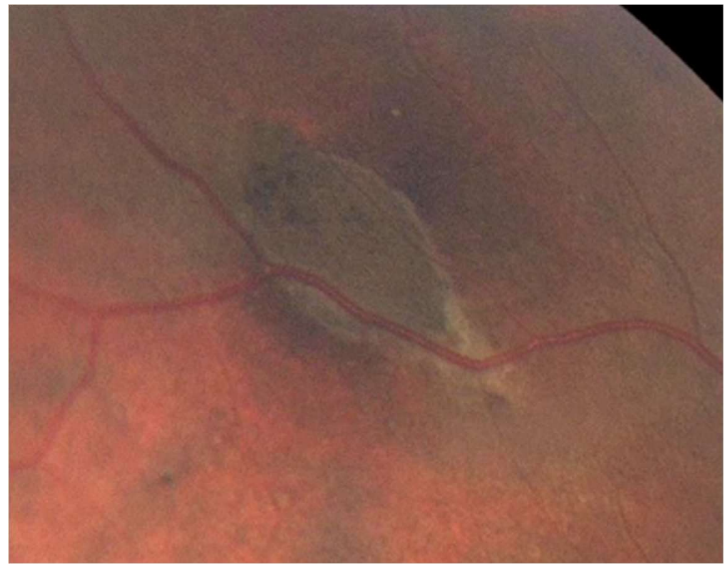


Figure 1a: Widefield retinal photos revealing multiple, flat pigmented lesions (white arrows) in multiple quadrants OD.

1b



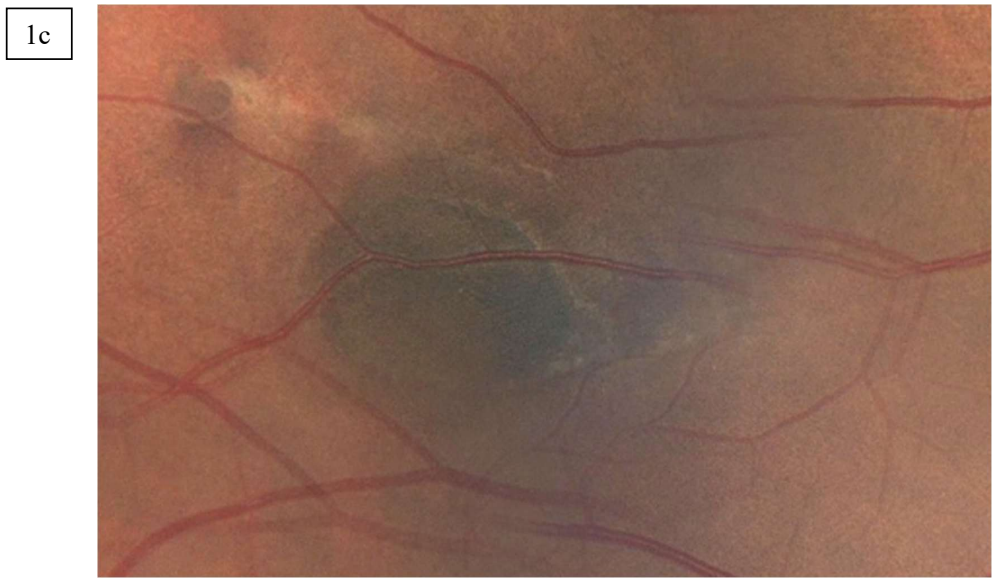


Figure 1b and 1c: Magnified view of the characteristic retinal lesion in Gardner Syndrome.

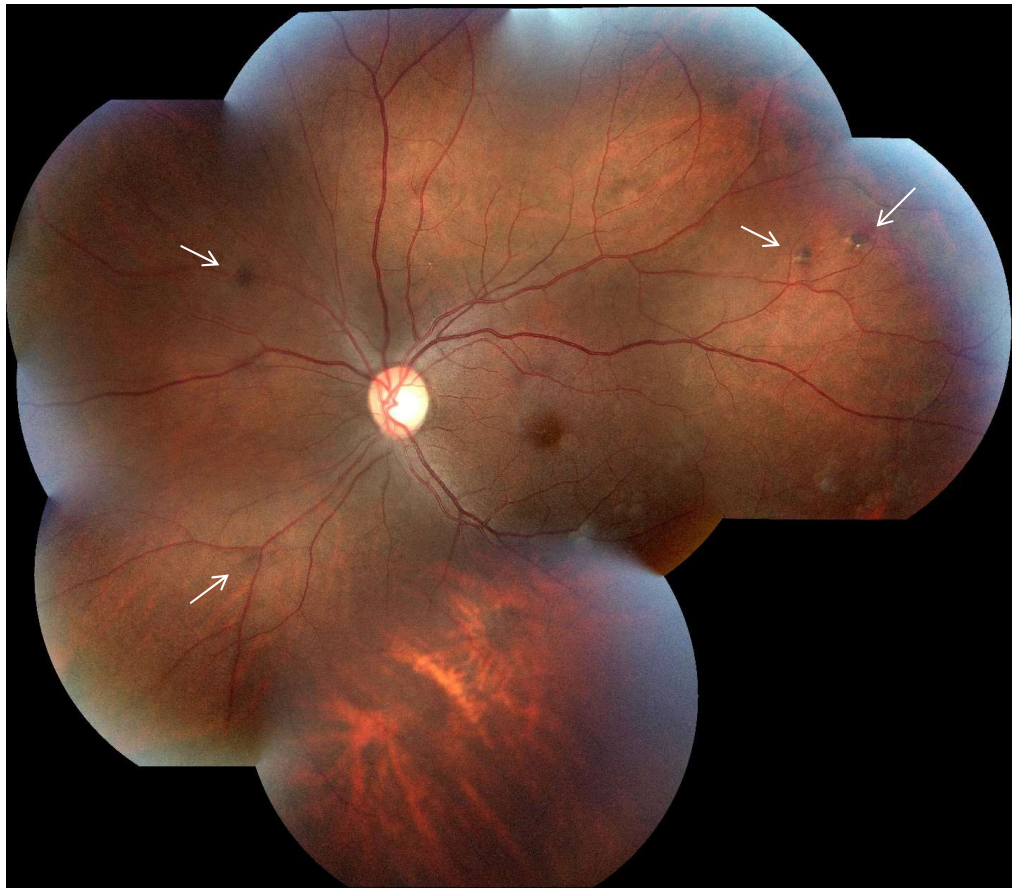


Figure 2: Widefield retinal photos revealing multiple, flat pigmented lesions (white arrows) in multiple quadrants OS.

Discussion

Extra-intestinal manifestations

While FAP primarily presents with colonic polyps, Gardner Syndrome as previously described, is characterized by additional extracolonic involvement. Intestinal involvement of Gardner Syndrome includes adenomatous polyps and carcinomas [2]. The extracolonic manifestations include desmoid tumors, osteomas, epidermoid cysts, fibromas, lipomas, dental abnormalities and ocular lesions [13,20].

These patients are at increased risk of extra-colonic malignancies such as duodenal and periampullary (3-5%), thyroid (2%) and pancreatic (2%). The syndrome is also associated several benign extraintestinal growths such as osteomas and dental abnormalities, cutaneous lesions, desmoid tumors, pigmented ocular fundus lesions, adrenal adenomas and nasal angiofibromas [13].

Ocular manifestations

Generally, a typical CHRPE lesion is a jet black, large, solitary, unilateral lesion with a well-defined smooth border demarcated with a pale halo and depigmented lacunae within the lesion [21]. The lesions associated with FAP are bilateral, multiple, present in multiple quadrants, more frequently found peripherally and smaller in size ranging from punctate lesions to multiple disc diameters [22,23]. The lesion is characteristically fusiform with a halo or a tail of depigmentation [24]. These lesions are different from Grouped Pigmentation of the Retina CHRPE where multiple small, pigmented lesions without halos ("bear tracks") are usually seen occupying one quadrant in one eye [3,24,25]. It is unlikely to see unilateral or singular lesions in FAP. In individuals with family history of malignant polyposis or colon cancer, if multiple bilateral fusiform CHRPE lesions with halo are present in multiple quadrants of the fundus, FAP should be suspected [9,22,24,25]. No retinal edema or subretinal fluid is associated with such lesions. Furthermore, the number of lesions observed may vary from individual to individual [21,26]. On histopathologic examination, the pigmented lesions usually involve a single layer of the retinal pigment epithelium; however, lesions can be multi-layered which is also distinct from a typical CHRPE [27].

In their analysis of 41 patients with Gardner Syndrome, Traboulsi et al. found that 37 (90.2%) patients had pigmented retinal lesions. Of these 37 patients, 32 (86.5%) had bilateral lesions and 5 (13.5%) had unilateral lesions. Lewis et al. found that of 43 patients in three families with strong histories of Gardner Syndrome, every individual examined with physical manifestations of the syndrome displayed ocular lesions (18 patients). Of the 24 patients with an ocular trait, 21 had bilateral lesions [28]. Sensitivities for certain criterion such as having at least four lesions on fundus examination with no restrictions on size have been reported at 68% [23].

There does not appear to be an association between the classic form of CHRPE and familial gastrointestinal cancer syndromes. It has been suggested that a more apt name for FAP-related ocular lesions could be retinal pigment epithelium hamartomas associated with familiar adenomatous polyposis (RPEH-FAP) or simply pigmented ocular fundus lesions (POFL) [22,26,29].

Management

Though the absence of multiple and bilateral RPEH-FAP or POFLs in a family does not exclude a diagnosis of FAP, its presence with typical characteristics can be an important clue early on in life pointing to a disposition towards a cancer-causing genotype prior to later presentation of more severe clinical findings suggestive of colonic malignancy. Such ocular findings in an individual with a suspect family history, should be referred to a gastroenterologist and for appropriate prognostication [3,21,24,28]. It has also been suggested that the presence of characteristic ocular lesions associated with FAP may predict an earlier onset of polyposis in patients compared to those who do not have the aforementioned typical lesion characteristics [30].

It is important to examine and screen patients suspected with FAP or Gardner Syndrome for POFLs [31,32]. The ophthalmologist can play an important role in early diagnosis of FAP if characteristic fundus findings are noted in a patient. More recently, Packo and Goldberg, have also described torpedo-like retinal lesions with Gardner's syndrome recommending that these patients also undergo evaluation of genotypic and phenotypic manifestations of the syndrome [19].

The mainstay of management of RPEH-FAP is periodic observation [3]. Visual acuity is not affected; however, if the pigmented lesions involve the macular area, deficits can be seen [21]. If there is growth or exudation associated with a solitary CHRPE, photocoagulation or cryotherapy can be utilized; however, exudation is rare. Periodic observation is generally recommended as growth, if it does occur, is slow [3].

Conclusion

The ophthalmologist can play a key diagnostic role prior to more severe clinical manifestations in patients with FAP. Recognizing numerous characteristic retinal lesions in both eyes in multiple quadrants, a potential biomarker for FAP, can allow for prompt referral and thorough work-up of an individual and their family.

Conflicts of Interest/Competing Interests

None of the authors have any proprietary interests or conflicts of interest related to this submission.

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