

## REVIEW

# Gardner syndrome: a mini review

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## ABSTRACT

Gardner syndrome is one of the hereditary gastrointestinal cancer syndromes and is not commonly encountered. It is a variant of familial adenomatous polyposis associated with cutaneous and soft tissue tumors. It is important to be aware of these syndromes as they are often associated with systemic manifestations and have implications for family members.

**Key words:** Gardner syndrome, gastrointestinal, tumors, gene

## INTRODUCTION

Gardner syndrome is one of the hereditary gastrointestinal cancer syndromes and is not commonly encountered. It is a variant of familial adenomatous polyposis (FAP) associated with cutaneous and soft tissue tumors.<sup>[1,2]</sup> FAP itself is characterized by the presence of  $\geq 100$  synchronous colorectal adenomas.<sup>[3]</sup> It is important to be aware of these syndromes as they are often associated with systemic manifestations (Table 1) and have implications for family members. Gardner syndrome was first reported in 1951 and involves the presence of numerous colonic polyps as well as extra-intestinal manifestations.<sup>[4]</sup> These include polyps in the small intestine along with epidermoid cysts, osteomas (mandible and skull), desmoid tumors, fibromatosis.<sup>[4]</sup> It is inherited in an autosomal dominant fashion and linked to the adenomatous polyposis coli (APC) gene.<sup>[4]</sup> Given the high risk and association with malignancy, identification and appropriate screening programs need to be initiated in order to prevent progression to malignancy or identify it in earlier stages. Patients with Gardner syndrome are at significantly higher risk for colorectal adenocarcinoma.<sup>[4]</sup>


## PATHOGENESIS

Gardner syndrome is linked to mutations in the APC gene, which is located on chromosome 5 within band 5q21.<sup>[4]</sup> APC is a tumor suppressor gene and encodes a protein and inactivation of this gene is one of the first steps in the colorectal cancer pathway in FAP.<sup>[5]</sup> The protein it encodes is a scaffolding protein that impacts the migration of cells along with cell adhesion. It is a component of a complex of proteins that modulates the phosphorylation and degradation of  $\beta$ -catenin.<sup>[6,7]</sup>  $\beta$ -catenin is an intracellular protein and it adheres to E-cadherin (a cell adhesion molecule) and joins E-cadherin to actin.<sup>[8]</sup> When  $\beta$ -catenin is phosphorylated, it signals ubiquitin ligases causing it to be degraded in the proteasome.<sup>[6,7]</sup> Mutation of the APC gene leads to accumulation of  $\beta$ -catenin builds up in the cytoplasm and it adhered to a family of transcription factors and causing changes to the expression of genes that are involved in differentiation, proliferation, migration and apoptosis.<sup>[6,7]</sup> APC also inhibits tumorigenesis, nurtures chromosomal stability by its effect on microtubules.<sup>[6,7]</sup> Inactivation of the APC gene causes damage to mitotic spindles, chromosomal instability leading to aneuploidy

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**Table 1: Intestinal and extra-intestinal manifestations of Gardner syndrome**

Gastrointestinal symptoms due to intestinal and colonic polyposis	Colorectal adenocarcinoma
Epidermal cysts	Ampullary cancer
Osteomas	Adrenal adenomas
Duodenal polyps and carcinoma	Hepatoblastoma
Papillary or follicular thyroid cancer	Dental abnormalities
Nasal angiofibromas	Gastric polyps

and promoting tumorigenesis.<sup>[5]</sup> Other changes that are potentially associated with Gardner syndrome include loss of DNA methylation, an aberration of the RAS gene (located on chromosome 12), aberration of TP53 gene (chromosome 17) and deletion of the colon cancer gene (chromosome 18).<sup>[9–11]</sup>

## CLINICAL FEATURES

The symptomatology of Gardner syndrome varies and can be linked to the presence of colonic and intestinal polyposis.<sup>[4]</sup> Symptoms could be secondary to obstruction from colonic polyposis with nausea, vomiting, constipation or could be gastrointestinal bleeding due to the polyposis with hematochezia.<sup>[4]</sup> Patients may be asymptomatic altogether and endoscopic examination performed for other indications may yield excess of polyps.<sup>[4]</sup> Epidermal cysts are one of the most common cutaneous features of Gardner syndrome and can occur at numerous sites (extremities, face, scalp).<sup>[12]</sup> Osteomas occur usually in the mandible though can also be seen in the skull and long bones.<sup>[12]</sup> They tend to be benign and also painless and are stated to antedate the diagnosis of intestinal polyposis.<sup>[12]</sup> Some of the other cutaneous manifestations include fibromas, nasal angiofibromas, lipomas and leiomyomas.<sup>[5]</sup> Supernumerary and impacted teeth are also noted in some patients as well.<sup>[13]</sup> One of the characteristic extra-colonic manifestations is congenital hypertrophy of the retinal epithelium (CHRPE) which is multiple, bilateral pigmented lesions in the fundus.<sup>[14]</sup> Patients are at high risk for malignancy especially colorectal adenocarcinoma as well as duodenal polyps and carcinoma, ampullary cancer, adrenal adenomas, hepatoblastoma, papillary or follicular thyroid cancer.<sup>[14,15]</sup>

## MANAGEMENT

The mainstay of therapy revolves around the screening and prevention of some of the outcomes associated with Gardner's syndrome. Screening for CRC should be performed by annual colonoscopy or flexible sigmoidoscopy starting at puberty.<sup>[3]</sup> Screening for proximal small intestine tumors should be performed with upper endoscopy with a side viewing scope to evaluate for duodenal polyps and duodenal cancer and

the ampulla and surveillance should be based on Spigelman staging for duodenal polyposis.<sup>[3]</sup> Upper endoscopy will also assess for gastric polyps as well and although most are benign fundic gland polyps, up to 1/2 may have associated dysplasia and rarely can advance to cancer.<sup>[16,17]</sup> Adenomatous gastric polyps may also be present on endoscopy in 10% of patients with FAP.<sup>[3]</sup> Annual assessment of the thyroid with a physical examination as well as an ultrasound should be started at the age of 10–20 years.<sup>[18]</sup> Biannual screening for hepatoblastoma with  $\alpha$ -fetoprotein and ultrasounds should be offered to affected infants until age 7 years.<sup>[3]</sup> Absolute indications for colorectal surgery in FAP include the diagnosis of colorectal cancer or suspicion for cancer.<sup>[3]</sup> Other more relative indications include a large increase in the number of adenomas, detection of multiple adenomas > 6 mm, high grade dysplasia in an adenoma or innumerable diminutive polyps preventing adequate surveillance.<sup>[3]</sup> Development of colorectal cancer ultimately occurs in FAP and timing of prophylactic colectomy is important in order to prevent this.<sup>[3,19]</sup>

Some of the other extra-intestinal manifestations and malignant conditions do not have clear cut screening programs and a clinician should be aware of those and their symptomatology and if concerns arises then evaluate accordingly.

## CONCLUSION

Gardner syndrome is a variant of FAP and is a hereditary colonic polyposis syndrome. Clinicians should be aware of this entity as it is associated with not only the risk for colorectal cancer but also extra-intestinal malignancy and other features. Recognition is key so that adequate screening programs can be implemented accordingly.

## DECLARATIONS

### Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

### Conflicts of interest

There is no conflict of interest among the authors.

## Data sharing statement

No additional data is available.

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