Gardner Syndrome Showing Multiple Osteomas in the Jaws

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Abstract

Gardner syndrome, an autosomal dominant inherited condition, is a subtype of familial adenomatous polyposis. It causes lesions in bones, skin, and teeth, as well as multiple gastrointestinal polyps, which, if left untreated, become malignant. Because patients with colorectal cancer have a low survival rate, early diagnosis and treatment of Gardner syndrome is critical. Therefore, the characteristic lesions of Gardner disease that appear on the face, jaws, and oral cavity must be understood; these can be evaluated by oral and maxillofacial clinicians. This report describes a case that was diagnosed and treated earlier with the help of a routine oral and maxillofacial examination and has had a seemingly good prognosis so far.

Key words: Gardner syndrome, Familial adenomatous polyposis, Osteoma

Introduction

Gardner syndrome is an autosomal dominant genetic disease caused by mutations in the adenomatous polyposis coli (APC) gene, located in the q21 to q22 of the fifth chromosome. These mutations increase the tumor factor known as β-catenin and can result in either cell cycle disorders or chromosomal instability[1,2]. This APC gene is the same gene that causes familial adenomatous polyposis (FAP), and Gardner syndrome is classified as a subtype of FAP. The colorectal manifestations of Gardner syndrome include adenomatous polyps in the colon, stomach, and small intestines and periampullary carcinoma similar to familial polyposis. Colorectal polyps begin to appear during puberty or in patients in their 20s; however, most are diagnosed when patients are in their 30s. When left untreated, all polyps become malignant by the time patients reach their 40s. Most late diagnoses are due to a late colonoscopy, which is performed when gastrointestinal symptoms such as anemia, intestinal hemorrhages, severe constipation, squeezing pain, stomach aches, diarrhea, intestinal obstructions, and mucus outflows are observed[1,3].

Gardner syndrome also refers to genetically inherited disorders in bones, skin, teeth, and eyes in addition to the multiple polyps found in the colon. In 1912, Devic and Bussy[4] were the first to describe patients with various soft tissue tumors that manifested extracolonically; these included fibromas, lipomas, neurofibromas, epidermoid cysts, and osteomas. In 1953, Gardner and Richards[5] reported that the inheritance pattern of these conditions was autosomal dominant and expressed in various ways. In a follow-up study in 1962, Gardner[6] reported that these
patients had abnormalities in their jaws and teeth, with complications that included impacted teeth, non-erupted teeth, congenitally missing teeth, supernumerary teeth, hypercementosis, dentigerous cysts, first and second molar root fusion, long and thin roots of the molars, and multiple caries and that 70% of the affected patients had some of these abnormalities[7].

Some of the extracolonic manifestations, including osteomas, may arise before development of colorectal disorders; therefore, early detection of these manifestations can advance the time of diagnosis of the syndrome. Among the manifestations, osteomas are known as a sensitive index for diagnosis and they are well detected by oral and maxillofacial clinicians. This case report also demonstrates that a routine oral and maxillofacial examination can aid in early diagnosis of Gardener syndrome[7,8].

Case Report

A 23-year-old female patient who had undergone extraction of her mandibular right and left third molar visited a dental clinic for a regular check-up. Radiographic evaluation revealed radiopaque bone findings in this patient’s jaws and she was referred to our hospital in December 2007. No special findings were observed six years earlier at the time of the mandibular right third molar extraction, and the patient had no familial or medical history of systemic disease. Panoramic radiograph showed multiple osteosclerotic findings in the maxillary and mandibular area, both maxillary third molars were in a fully erupted state, and no findings of other impacted teeth, deciduous teeth retention, or odontoma were observed (Fig. 1).

Enhanced facial computed tomography (CT) and a three-phase bone scan were performed. No contrast-enhanced area was found on the CT scan; however, a multifocal radiopaque mass with opacity similar to that of the cortical bones and teeth was found. No radiopaque lesions involving other parts of the skull, such as the orbit, nasal cavity, or maxillary sinus were noted. No cortical thinning or expansion was found (Fig. 2). Results of bone scan did not show any abnormally increased absorption of radioactive isotopes (99mTc-methylene diphosphonate) in the jaws or joints.

Based on the radiographic findings, the patient was pre-diagnosed with florid cemento-osseous dysplasia or multiple osteomas, and because it was not a single lesion, the patient was referred to the Department of Gastroenterology for differential diagnosis of Gardner syndrome. Gastroendoscopic findings showed 5 to 10 multiple color-

![Fig. 1. Panoramic image taken at the patient’s first visit shows multiple sclerotic osteomas in the mandible and maxilla. Compared to the mandible, diagnosis of the maxilla is more difficult. No other findings of dental abnormalities were found in the jaw, except osteoma.](image1)

![Fig. 2. Facial computed tomography image showing osteoma limited to the mandible (A) and maxilla (B). No growth out of the cortical bone of the jaw was found, a solitary form of multiple osteoma was observed, and was diagnosed as endosteal osteoma. No osteoma was found in the paranasal sinus or skull.](image2)
ectal polyps; five of these were removed, and the patient was diagnosed with Gardner syndrome (Fig. 3). Over the course of four years, a total of 18 polyps were removed, and one year after the final removal of polyps, no polyps were found on the endoscopic scan. A thyroid ultrasound performed two years after the first visit showed a nodule in the left lobe. A biopsy performed 18 months later confirmed papillary carcinoma, and a left lobe thyroidectomy was performed.

The patient revisited our department during the third year for a regular checkup, and microscopic bone changes were suspected in the apex area of the mandibular left second molar, which had recently undergone endodontic treatment. Conebeam CT was performed for follow-up observation, however, no obvious changes were observed. During the regular checkup, caries were found in both maxillary third molars, which were therefore designated for extraction. Although the teeth were extracted from the maxilla, the luxation was relatively difficult, and part of the alveolar bone was removed with the teeth. The alveolar bone was separated from the removed teeth for biopsy. A dense, lamellar bone-like finding was observed in the biopsy, and it was diagnosed as an osteoma. The extraction sites were relatively well-healed without specific findings after tooth extraction (Fig. 4). No changes in the face or radiological findings were observed at the four, five, and six-year follow-ups.

Discussion

Prevalence of Gardner syndrome varies from 1 per 8,300 or 16,000, and 30% of affected patients have spontaneously developed genetic mutations[1]. Unfortunately, there are no accurate statistics for Gardner syndrome in Korea; some studies have been conducted on patients and families with familial polyposis only. Since 1990, after establishment of the Korean hereditary tumor registry, familial polyposis examinations have been performed on 104 families, and in 1991, Park et al.[9] conducted a study on a large number of patients, analyzing 74 patients and 72 families diagnosed as having colonic polyposis. The average age of patients was 38 years old, and 46% of them had family history of colonic polyposis. Common factors other than colon disease included bone abnormalities (8%), duodenal adenomas (8%), congenital hypertrophy of the retinal pigment epithelium (7%), and dental abnormalities (7%). Among these patients, three were diagnosed with Gardner syndrome and had bone tumors, epidermoid cysts, and

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dental abnormalities. In a study reported by Lee et al.[12] in 2006, which included 40 patients with FAP, the average age of patients was also 38 years, and 42% of them had a family history of FAP. Extracolonic diseases included mandible osteomas (5.1%), retinal cell hyperplasia (7.5%), thyroid cancer (5.1%), desmoid tumors (7.7%), and duodenal adenomas (5.9%), and two patients were diagnosed with Gardner syndrome. Based on only these two studies, the average age of the diagnosed patients was the late 30s, 5% to 8% of the patients have jaw abnormalities, and approximately 4% of FAP patients in Korea have Gardner syndrome.

According to international guidelines, diagnostic criteria for FAP include more than 100 colorectal adenomas, regardless of family history or colorectal cancer[2]; however, diagnosis of Gardner syndrome can be made through genetic testing or colonoscopy for mutations and multiple polyp findings after confirming clinical manifestations of dental abnormalities or osteomas on dental radiography. This is possible because the oral cavity or maxillofacial findings appear years before development of intestinal polyps[3]. As mentioned, without proper treatment, colon polyps become malignant 100% of the time; thus, early diagnosis of this disease is essential. Therefore, clinicians who treat the oral and maxillofacial area need to understand the extracolonic findings, such as osteomas, dental abnormalities, and soft tissue disorders that frequently occur in the jaws or in the facial area.

Approximately 90% of patients with Gardner syndrome have skeletal abnormalities in the jaws, and, among these, osteomas are the most common finding. Common sites for osteomas are the outer cortex of the skull, the paranasal sinus, and the mandible. These osteosclerotic findings in the jaw are infrequent in healthy adults, however, more than 70% of patients with Gardner syndrome have them[10,11]. Ida et al.[12] stated that Gardner syndrome can be suspected when more than three osteomas are present. Medical treatments are not required for osteomas that do not have symptoms, however, for those that cause severe expansion in the jaws leading to facial asymmetry, surgery can be considered for aesthetic purposes[3,13,14]. In the current case, facial CT was used for observation of osteomas that developed in multiple ranges; they were observed to have limited development in the mandible and maxilla and did not cause any facial deformities (Fig. 2).

Gardner syndrome generally involves compact osteomas, not the cancellous type, and each histologic characteristic is equal to that of solitary osteomas, even in multiple osteomas[1]. In the current case, the histologic examination performed at the time of the third maxillary molar extraction also showed a dense lamellar bone, which can have the appearance of a compact osteoma (Fig. 4). Although a slowly growing osteoma enters a dormant period as it reaches a fixed size, Takeuchi et al.[15] reported that both the size and number of jaw lesions, including osteomas, in patients with Gardner syndrome can increase, and these can occur gradually even after adulthood, This makes long-term follow-up of osteomas meaningful even after Gardner syndrome is diagnosed.

Multiple osteomas play an important role in diagnosis of Gardner syndrome. However, radiographic evaluation is somewhat difficult since other radiopaque lesions, such as odontogenic neoplasms, fibro-osseous lesions, osteoblastomas, cementoblastomas, and exostosis, have an ap-

| Table 1. Differential diagnosis of radiopaque lesions from osteomas |
|----------------------------------|----------------------------------|
| Radiopaque lesions               | Osteomas                         |
| Initially, such lesions are radiolucent and progress to ill-defined, | No radiolucent initial stage |
| ground glass-like opaque lesions  | Osteomas can continue to grow gradually, even after adulthood |
| They commonly stop growing after adulthood                      | Commonly asymptomatic               |
| Osteoblastomas                  | Osteosclerosis is found around the margins of the lesions |
| Accompanied by pain and swelling                       | These lesions are not related to the teeth |
| Well-defined margins with radiolucent halos                 | No symmetrical pattern               |
| Cementoblastomas                | They are usually found in the mandible, but they can be found other parts of the skull, such as paranasal sinus, frontal sinus, or condyle |
| Cementoblastomas involve the teeth                            |
| Exostosis                       |                                  |
| It commonly appears bilaterally and is found in a specific anatomical area |                                  |
| It ceases to grow after puberty                                |                                  |
pearance similar to that of osteomas. Thus, differential diagnosis of these disorders may be required (Table 1)[14]. In addition, if a patient with multiple osteomas has other manifestations, the possibility of Gardner syndrome should be evaluated by genetic testing or colonoscopy (Table 2).

Although the current case had no dental abnormalities, they are often found in patients with Gardner syndrome; approximately 30% of patients have supernumerary teeth, odontomas, impacted teeth, and congenital missing teeth[10]. Impacted teeth can be extracted for therapeutic purposes when needed. Ramaglia et al.[16] reported that tooth extraction is difficult in patients with Gardner syndrome because the alveolar bone is quite compact and the periodontal ligament space almost disappears due to hypercementosis. In the current case, panoramic and conebeam CT images showed partially atrophied periodontal ligaments, and proper luxation of the maxillary tooth extraction was somewhat difficult. However, the recovery was no different from that of a normal extraction socket.

Although not found in this case, similar to the dental abnormalities commonly found in patients with Gardner syndrome, many patients have skin diseases; the most common findings are epidermoid cysts. These lesions are found earlier than general skin cysts. They are found in puberty, in uncommon areas such as the arms, legs, face, and scalp; therefore, these lesions can also be useful in diagnosis of Gardner syndrome. The lesions are exposed and can also be well detected by oral maxillofacial clinicians during routine examinations. In most cases, the lesions are asymptomatic, however, they can develop into the suppurative type and burs[3,8]. Other skin lesions include fibromas, neurofibromas, leiomyomas, lipomas, and desmoid tumors[1,3].

Although not well known, there is also an increased prevalence of thyroid carcinoma; the prevalence in women has been reported to increase by more than 100 fold[1]. According to Tomoda et al.[17], FAP can be diagnosed early, as they reported a very rare case of a cribriform-morular variant showing papillary thyroid carcinoma before diagnosis of colon cancer related to FAP. In the current case, the thyroid ultrasound performed at the initial examination showed no specific findings; however, papillary thyroid carcinoma was found in the left lobe 3.5 years later, and, therefore, thyroid resection was performed.

The colorectal manifestations of Gardner syndrome are the most critical and fatal to patients, and should be evaluated urgently for prevention of malignancy. Gayther et al.[18] stated that prophylactic resection should be performed before the age of 25 in order to prevent colon cancer when a patient is diagnosed with FAP. In general, when more than 20 or 30 adenomas are found or biopsy findings indicate multiple adenomas, a colectomy is recommended[19].

In this case, a total of 18 polyps have been removed at the time of this report; among these, 13 polyps were adenomatous. Out of 13 polyps, 12 were tubular adenomas, and only one specimen was a tubulovillous adenoma. Adenomatous polyps are classified according to three types: tubular, tubulovillous, and villous. Tubular adenomas, the most frequently found type of adenoma, are unlikely to become malignant. Villous adenomas, which frequently occur in the rectum, are usually larger in size than the other two types of adenomas and have the highest morbidity and mortality rates among all polyps. Tubulovillous adenomas fall between the two types in terms of their morbidity and mortality rates. Therefore, this case was found to be in a relatively mild stage, and conservative treatment was possible.

In the current case, multiple osteosclerotic findings were found in the patient’s jaws in the early stage of the syndrome, and the patient was treated immediately by the gastroenterology department through gastroendoscopy. As a result, the patient was diagnosed with Gardner syndrome in her early 20s. This is approximately 10 years earlier than the average diagnosis and 20 years earlier than the average time for development of malignancy. The patient

Table 2. Clinical and radiographic findings that may represent Gardner syndrome

| Oral and maxillofacial abnormalities | Multiple osteomas: more than three lesions |
| Multiple osteomas found in the skull and long bones |
| Multiple osteomas accompanied by dental abnormalities |
| Family history of osteoma or dental abnormalities |
| Accompanied by other manifestations |
| The gastrointestinal system: adenomatous polyps in the colon and rectum |
| Dermatology: epidermoid cysts, lipomas, lipofiromas, desmoid tumors |
| Endocrine system: papillary thyroid cancer |
| Ocular system: congenital hypertrophy of the retinal pigment epithelium |
was diagnosed at a very early stage, considering the fact that she had no family history. Among the extracolonic manifestations, skeletal and dental disorders in the jaws, such as osteomas and dental abnormalities commonly affect patients with Gardner syndrome and they are found in early stages of the syndrome. These maxillofacial disorders can be well evaluated by oral and maxillofacial surgeons. Although Gardner syndrome is classified as a rare disease, its late diagnosis can be quite detrimental for patients; therefore, maxillofacial clinicians’ attention to this issue is critical.

References