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Hamartomatous Gastric Polyposis in a Patient with Tuberous Sclerosis

A 42-year-old female diagnosed with tuberous sclerosis was found to have multiple polyps in the fundus of stomach. On histologic examination, the lesions were hamartomatous polyps. In tuberous sclerosis, many lesions occur in multiple organs and there are several reports about the frequent association of hamartomatous polyps of the colon. However, gastric manifestation of tuberous sclerosis has not been established probably due to its asymptomatic nature. This is the first report of multiple gastric hamartomatous polyposis in patient with tuberous sclerosis.

Key Words: *Tuberous Sclerosis; Polyps; Stomach; Hamartoma*

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INTRODUCTION

Tuberous sclerosis is an autosomal dominant disease manifested by the clinical triad of seizure, mental retardation and adenoma sebaceum (1-3). Clinical manifestations are skin lesion, brain lesion, renal lesion, cardiac lesion, gastrointestinal lesion and so on (4). Recently, rectal hamartomatous polyposis is regarded as one of the significant clinical manifestations of tuberous sclerosis (5, 6). However, gastric polyposis has not been described yet. Here, we describe a case of gastric polyposis in tuberous sclerosis patient.

CASE REPORT

A 42-year-old female was treated at Seoul National University Hospital since 19 years ago. She manifested episodic seizure and had adenoma sebaceum on her face since the age of five. Mentality was within the normal range. Brain computed tomography revealed multiple subependymal calcific nodules (Fig. 1). No other family member showed evidence of seizure or adenoma sebaceum. She received treatment for renal artery embolization of the right kidney and nephrectomy of the left kidney due to angiomyolipomas at 24 and 25 years-old, respectively. She suffered from recurrent attacks of chest pain and dyspnea since 9 years ago. Chest roentgenography revealed reticulonodular haziness in the bilateral lower lungs complicated with pneumothorax which was considered to be lymphangioleiomyomatosis. Eight years ago, she received treatment for hepatic artery embolization due to the rupture of angiomyolipoma of the liver. Gastroscopic examination performed during that period showed multiple elevated lesions and ulcerations in the esophagus and multiple polyps in the fundus of the stomach. Histologically, the lesions of the stomach showed mild degree of chronic inflammation in the lam-

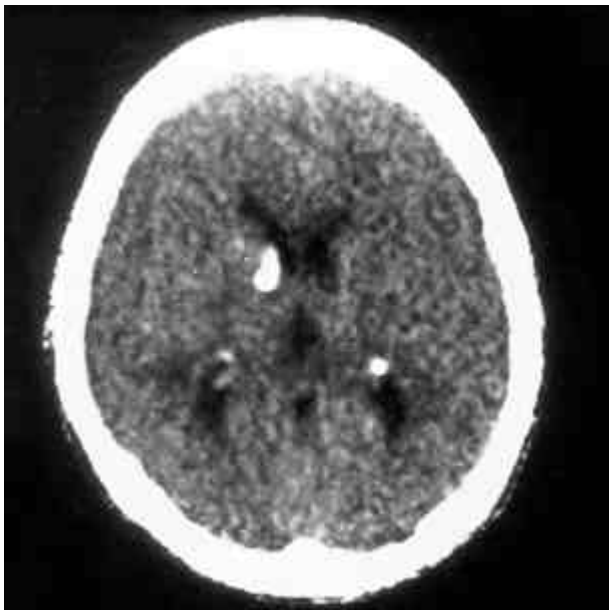

Fig. 1. Computed tomography of the brain. Multiple calcific nodules are noted at the subependymal region.

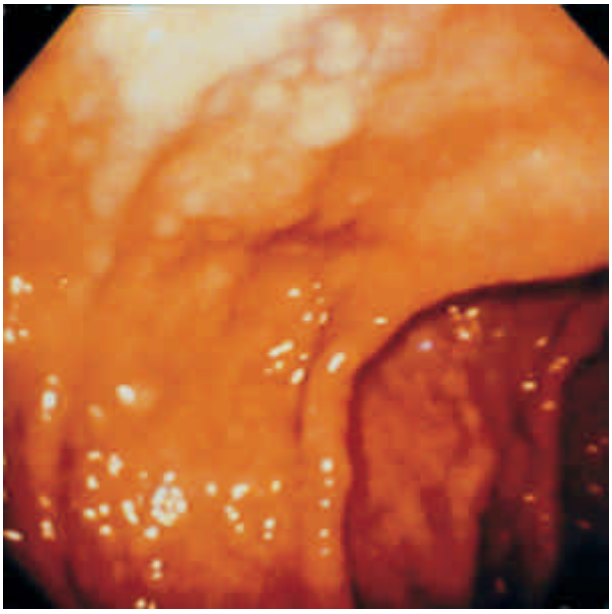

Fig. 2. Gastrofiberscopic finding of the patient. Numerous whitish polyps are diffusely scattered on the fundic mucosa.

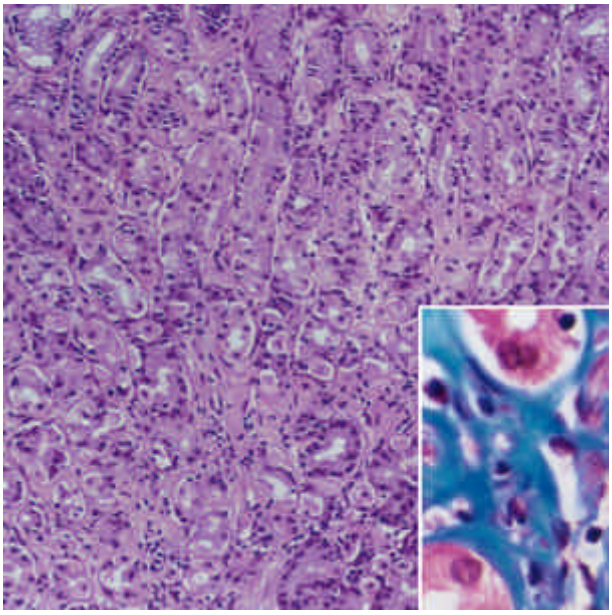

Fig. 3. Microscopic finding of the gastric polyp. Smooth muscle bundles between fundic glands are noted in the lamina propria (H&E, ×100). Inset: High power view of Masson-Trichrome staining (×400).

ina propria and those of the esophagus showed infiltration of acute inflammatory cells and proliferation of blood vessels and fibroblasts.

Six months ago, she experienced aggravation of seizure and lower abdominal pain. On brain MRI, there were ill-defined lesions showing low signal intensity in both T1 and T2 weighted images at the left frontal convexity

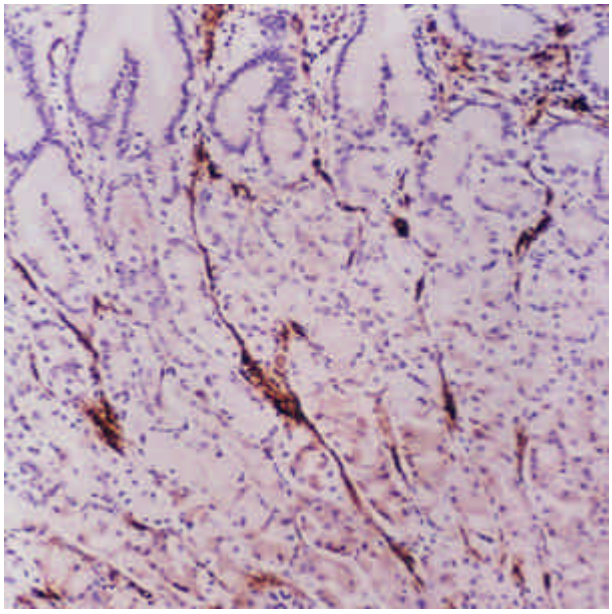

Fig. 4. Immunohistochemical staining for smooth muscle actin. Smooth muscle bundles are prominent in the lamina propria and clearly reach up to the surface epithelium (×100).

of the cerebrum, consistent with findings of cerebromalacia. A well defined 3-cm sized mass which showed low signal intensity in T1 weighted image and iso-signal intensity in T2 weighted image, was detected at the nasopharynx of the patient. On biopsy, it showed scarce fibroblastic proliferation in dense hyalinized collagenous stroma. On double contrast barium study, there was no abnormal lesion at the large intestine except for an about 1-cm sized peduculated polyp at the cecum. On gastroscopic examination, numerous polyps were recognized at the fundus of the stomach (Fig. 2). No abnormal mucosal lesion was found at the esophagus and the duodenum. Gastroscopic biopsy of the fundic polyps was done. Histologically, the lesion showed mild hyperplasia of gastric gland and prominent smooth muscle proliferation in the lamina propria (Fig. 3). Immunohistochemical staining with anti-smooth muscle actin antibody (dilution-1:100, DAKO) highlighted smooth muscle bundles reaching to the surface epithelium, confirming the hamartomatous nature of these polyps (Fig. 4).

DISCUSSION

Since the first description of tuberous sclerosis by von Recklinghausen (3), the classical triad including facial angiofibroma, epilepsy and mental retardation was established (1-3). However, half of the patients do not show dermatologic or neurologic signs, which is known as "forme fruste" (3). Classical signs regarded as pathogno-

monic for tuberous sclerosis are now considered to be less specific and there is no single clinical or radiologic feature which is absolutely specific for tuberous sclerosis (8). Because tuberous sclerosis is a genetic disease involving multiple organs, a definite diagnosis depends on two or more lesions of different types, rather than multiple lesions of the same type in the same organ (8). Two genes, *TSC1* and *TSC2*, associated with tuberous sclerosis have been identified (9, 10). *TSC1* is mapped at chromosome 9q34. The product of *TSC1* gene is hamartin, the function of which is not well understood. The product of *TSC2* is tuberin, which contains GTPase activating protein (GAP)-related domain (11). Tuberin with GAP activity plays a role in cell division and neuronal differentiation through the signal pathway of Ras superfamily, rap1 and rab5 (12, 13). Meanwhile, 60-70% of tuberous sclerosis occur sporadically which is supposed to be caused by de novo mutation (7, 8).

In tuberous sclerosis, the entire gastrointestinal tract from mouth to rectum can be involved. According to the literature, oral manifestations consist of fibroma, fibrous hyperplasia, papilloma, hemangioma and pitted enamel hypoplasia (14, 15). Fibrous tumor has been reported in the esophagus. In our case, fibrous hyperplasia was found in the lesion of nasopharynx. In the small intestine, duodenal mucoviscidosis has been described (18). Vascular malformations, angiomyolipoma, hamartomatous polyps, adenomatous polyps and adenocarcinoma have been reported in the colon (14, 17).

Gastric manifestations in tuberous sclerosis are usually asymptomatic so that special examinations are not required routinely. Therefore, the exact nature of gastric lesion is not well known. A large gastric tumor described as "mixed tumor" by van Bouwdijk-Bastiaanse in 1933 was the first report on gastric lesion in tuberous sclerosis (14, 16). In the report by Devroede et al. in 1988, only one patient had a hyperplastic polyp in the stomach among 12 patients with tuberous sclerosis subjected to thorough gastrointestinal investigation (5), which may be coincidental because of its high incidence in normal population. In 1994, Hizawa et al. reported that one of the two patients with tuberous sclerosis had eight hamartomatous polyps in the stomach (17). The polyps were distributed at the gastric body and showed hyperplasia of foveolar epithelium without any cystic change of gland. In our case, numerous hamartomatous polyps were diffusely scattered throughout the fundus of the stomach. To the best of our knowledge, the present case is the first report of hamartomatous gastric polyposis manifested in patient with tuberous sclerosis. By the way, fundic gland polyp is one of the most frequent hamartomatous lesion of the stomach. The hamartomatous polyp in our case differs from the fundic gland polyp, in terms of the histologic features. For example, the fundic gland polyp shows disorganized glandular proliferation such as convolution, curving, branching and cystic dilation of fundic glands.

We believe that the polyposis in the stomach of this patient is a manifestation of tuberous sclerosis rather than coincidental finding, because this kind of hamartomatous lesion is extremely rare. Furthermore, similar lesions were reported in the colon of tuberous sclerosis patients (5, 6). Recently, rectal hamartomatous polyposis is accepted as one of the clinical manifestations of tuberous sclerosis (5, 6). However, to accept hamartomatous gastric polyposis as a phenotypic marker of tuberous sclerosis, more clinical information is needed.

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