Neurofibromatosis type 1-associated multiple rectal neuroendocrine tumors: A case report and review of the literature

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Neurofibromatosis type 1 (NF-1) is commonly associated with benign or malignant tumors in both the central and peripheral nervous systems. However, rare cases of NF-1-associated multiple rectal neuroendocrine tumors have been reported. This report describes a case of a 39-year-old female with NF-1 and intermittent hematochezia as a primary symptom. Physical examination showed multiple subcutaneous nodules and café au lait spots with obvious scoliosis of the back. Imaging examinations and colonoscopy found malformation of the left external iliac vein and multiple gray-yellow nodules with varying sizes and shapes in the rectal submucosal layer. Histological and immunohistochemical results suggested multiple rectal neuroendocrine tumors, a rare disease with few appreciable symptoms and a particularly poor prognosis. The patient with NF-1 presented here had not only multiple rectal neuroendocrine neoplasms but also vascular malformations, scoliosis and other multiple system lesions. This case therefore contributes to improving clinical understanding, diagnosis and treatment of related complications for patients with NF-1 who present with associated medical conditions.

Key words: Neurofibromatosis type 1; Multiple rectal neuroendocrine tumors; Vascular malformations; Scoliosis
A 39 year old woman was admitted to our department because of intermittent bloody stools without vomiting, abdominal pain, diarrhea, skin flushes, etc. The patient had suffered from a slightly curved spinal column since childhood, with the abnormal curvature becoming noticeable 13 years prior. Systemic skin pimples then occurred gradually without pain or itching. Physical examination showed multiple hemispherical subcutaneous nodules with varying sizes and soft and clear boundaries on the chest and abdomen. There were coffee pigment spots with varied sizes and colors between these nodules, with a maximal size of 3 cm × 2 cm (Figure 1A). The patient’s father also had definitive NF-1. Blood examination showed the hemoglobin level of the patient was 101 g/L, with no other abnormalities. Computed tomography and magnetic resonance imaging (MRI) of the chest revealed enlarged mediastinal lymph nodes, dermatologic nodules with long T1 and T2 values, uniform densities, clear boundaries, diameters of < 10 mm (Figure 1B), thoracolumbar scoliosis and thoracic deformities (Figure 1C-D). A pelvic MRI detected segmental thickening of the right external iliac vein, with a thickness of 27.4 mm and a sausage-like appearance (Figure 2). The middle and lower rectal mucosae were irregularly thickened, with 26.5 mm at the widest point and an irregular signal with long T1 and slightly longer T2 values. Obvious uneven enhancement was noted in the post-contrast arterial phase, while separation and necrosis were visible in parts. These presentations suggested a diagnosis of multiple rectal lesions (Figure 3A and B). No obvious abnormalities were noted in the computed tomography of the head. Colonoscopy revealed multiple yellow-white nodular uplifts under the rectal mucosa at approximately 1-10 cm from the anal verge. These uplifts varied between 0.3-2.5 cm in diameter and presented with a patchy distribution. The lesion involved the entire rectal lumen (Figure 3C and D). The uplifted surface was smooth but congestive, and blood vessels were apparent on the surface of the nodules under the narrow-band imaging (Figure 3E). Endoscopic ultrasound revealed multiple hypoechogenic lesions in the mucosa and submucosa, with enlarged lymph nodes in the outer membrane (Figure 3F). Pathohistological and immunohistochemical examinations (n = 10) at many sites from rectal samples showed that tumor cells were present in the lesions and mutually linked to form cord, nest, or gland-like structures. The tumor cells were round, oval or columnar; of varying sizes, with round nuclei, and without obvious mitosis. Cells were CD117 (+), CD56 (+), CK (+), CgA (+), Syn (+), and TTF-1 (-), with a Ki-67 index of < 2%, thus supporting the diagnosis of a grade 1 rectal neuroendocrine tumor (Figure 4A-B). Specimens from many nodules were taken throughout the body and were examined by pathohistology and immunohistochemistry. The subdermal nerve fibers were in a disordered arrangement, and the cells were elongated, spindle-shaped and oddly distributed in the light-stained collagen matrix. Immune staining revealed CD34 (+) and S-100 (+) expression, deep and S-shaped
nuclei, and scattered mast cells. These pathological features corresponded to a diagnosis of type I neurofibromatosis (Figure 4C-E). This patient had multiple rectal neuroendocrine tumors with a diameter > 20 mm. The probability of lymph node metastasis and distant metastasis was considered to be very high. Surgical intervention was advised, however the patient rejected surgery and favored surveillance by regular follow-ups every 3-6 mo.

DISCUSSION

NF-1 is an autosomal dominant genetic disorder caused by abnormal ectodermal development that results in peripheral and central nervous system impairment. This disease has a 68.6% and 31.4% likelihood of maternal and paternal heritability, respectively. The etiology of NF-1 is not fully understood. NF-1 is currently considered to be related to gene mutations, hormones, telomerase, angiogenic factors, tumor microenvironment, electrophysiological changes and other factors related to tumor promotion [7]. Neurofilament, encoded by the NF-1 gene, is a negative regulator of the Ras pathway, and the GAP-related domains encoded by exons 21-27 are homologous to the GTPase-activating protein family. This protein may convert the active form of Ras-GTP into the inactive form of Ras-GDP, thereby inhibiting the activation of Ras and its downstream signaling pathways including Raf-MEK-ERK and Paf-MAPK-PI3-K/Akt [6,7]. Therefore, patients with an NF-1 mutation could present with complications such as spinal malformations, vascular malformations, and benign and malignant tumors in both the central and peripheral nervous systems due to excessive Ras pathway activation. The clinical symptoms are diverse, complex and difficult to treat. Neuroendocrine tumors refer to a group of heterogeneous tumors that originate from neuroendocrine cells. They grow slowly with malignant potential and can occur in multiple systems throughout the body, although they are most commonly found in the gastrointestinal tract [14]. Clinical data confirmed that approximately two percent of patients diagnosed with NF-1 also have neuroendocrine tumors, which may be related to Ras-PI3K over-activation that leads to an imbalance of rapamycin (mTOR) expression [15]. The case presented in this report contradicts previous studies claiming that complicated neuroendocrine tumors are commonly located in the region around the ampulla of the duodenum and pancreas [9-12]. There are very few cases of NF-1 that are associated with multiple rectal neuroendocrine tumors. Rectal neuroendocrine neoplasms (NENs) are often derived from peptidergic neurons and neuroendocrine cells of the rectal mucosal epithelium, and are often divided into functional or non-functional types [16]. The clinical symptoms of functional NENs are most often related to peptides and hormones secreted from the primary site, while non-functional NENs have no specific clinical symptoms. Imaging, endoscopic ultrasound and biopsy are used as the main diagnostic methods for non-functional NENs.

Clinically, the rectal neuroendocrine tumors are mostly non-functional. In addition, rectal neuroendocrine tumors are usually single-onset, with only two to four percent being multiple-onset. Previous research suggests that the MEN1 (neuroendocrine tumor) gene, PI3-K/AKT, Raf/MEK/ERK, Notch, GSK-3β and other signaling pathways may be involved in the occurrence and metastasis of multiple rectal tumors [17]. We have summarized the relevant literature in the past 20 years and found that only one case, combined with NF-1 in 14 cases, reports of multiple rectal neuroendocrine tumors.
Surgical treatment. In addition, in light of the malignant tendency and metastasis of most gastrointestinal NENs, in addition to surgery, rectal neuroendocrine tumors require a combination of multidisciplinary and multiple interventions. For example, somatostatin analogs and molecular targeting drugs like sunitinib and everolimus inhibit tumor growth, are anti-angiogenic, and have been successfully applied in clinical applications. Additionally, the chemotherapeutic drug streptozocin, as well as similar types of temozolomides, have certain effects on patients who have failed with standardized treatments of neuroendocrine carcinomas. In recent years, peptide receptor-mediated radio receptor therapy has proven to have a definite effect on alleviating symptoms and shrinking tumors, however its severe side effects restrict its use and promotion. Although the long-term effects of the aforementioned adjuvant therapies are still not fully confirmed, multidisciplinary and multi-system combination therapy is an inevitable trend in the treatment of neuroendocrine tumors. However, the patient rejected surgery and so the pathological data are therefore not available in this case. The risk of malignancy and metastasis in this patient is very high, and she should receive regular follow-ups every 3-6 mo.

In addition to rectal neuroendocrine tumors, the patient also presented with malformations of the external iliac veins and the spinal column. A pelvic MRI revealed segmental thickening of the right external iliac vein, which was nearly double the normal diameter.

Figure 3 Imaging, endoscopy and endoscopy ultrasonographic findings of multiple rectal neuroendocrine tumors in the patient. A and B: Magnetic resonance imaging (red dotted line marking the widest point of the tumors, measuring approximately 26.5 mm); C and D: Endoscopic manifestations; E: Blood vessels were apparent on the surface of the nodules under the NBI (neuroendocrine tumors marked by the white arrow); F: Endoscopic ultrasonography of the multiple rectal neuroendocrine tumors (red dotted line marking the widest point of the tumors, measuring approximately 25.5 mm). NBI: Narrow-band imaging.
and showed a sausage-like appearance. However, there was no obvious stenosis below the venous expansion, suggesting a congenital deformity instead of a compensatory increase caused by stenosis. Neurofibromatosis is associated with a one to three percent risk of vascular lesions. The lesions can affect varying sizes of blood vessels and present as stenosis, occlusions, hemorrhages, aneurysms, arteriovenous malformations and arteriovenous fistulas. The renal artery is the most vulnerable blood vessel, followed by the superior mesenteric artery, intracranial artery, cardiovascular, etc[29]. NF-1 patients often present with hypertension or arteriovenous malformations and bleeding prior to definitive diagnosis. To our knowledge, this is the first case of NF-1 that is complicated with abdominal iliac vein malformation. Previous studies have suggested that vascular dysplasia may be associated with mutations in the NF-1 gene, which may lead to dysregulated vascular development in the mesoderm. Concentric growth, rupture of elastic fibers, and nodule hyperplasia occur in the intima of blood vessels. The reduction of smooth muscle, decrease in elastic components in the media, and increase in brittleness of the vessel wall are all observed, ultimately leading to thinning of the blood vessel wall, poor elasticity, and formation of a large number of sinus cavities in the diseased tissue, which can cause bleeding[29,30]. Currently, the preferred treatment for vascular malfor-

### Table 1 Summary of multiple rectal carcinoid case reports

| Case               | Sex | Age | Number | Size (mm) | The depth of invasion | Lymph node metastasis | Histological stage | Treatment | Complicated with NF-1 |
|--------------------|-----|-----|--------|-----------|-----------------------|-----------------------|---------------------|-----------|----------------------|
| Kato et al[26]     | M   | 61  | 52     | 1-6       | SM                    | NA                    | NA                  | NA        | No                   |
| Maruyama et al[18] | M   | 52  | 5      | 4-10      | M3                    | No                    | NA                  | NA        | AR                   |
| Okamoto et al[20]  | M   | 54  | 4      | < 6       | SM                    | NA                    | NA                  | NA        | ESMR-L               |
| Haraguchi et al[22]| M   | 69  | 30     | < 10      | SM                    | Yes                   | NA                  | AR        | No                   |
| Sasa et al[31]     | M   | 51  | 7      | < 8       | SM                    | Yes                   | GI                  | AR        | No                   |
| Muh et al[27]      | M   | 58  | 3      | < 7       | M3                    | Yes                   | C2                  | AR        | No                   |
| Zhou et al[23]     | M   | 47  | 3      | 5-8       | SM                    | No                    | G1                  | TEM       | No                   |
| Park et al[24]     | M   | 52  | 2      | 4         | SM                    | No                    | G1                  | ESMR-L    | No                   |
| M                  | M   | 32  | 3      | 5-7       | SM                    | No                    | G1                  | ESMR-L    | No                   |
| F                  | F   | 65  | 3      | 5-7       | SM                    | No                    | NA                  | EMR       | No                   |
| M                  | M   | 62  | 2      | 5         | SM                    | No                    | G1                  | ESMR-L    | No                   |
| F                  | F   | 48  | 2      | NA        | SM                    | No                    | G1                  | ESMR-L    | No                   |
| Hua et al[25]      | F   | 61  | 12     | 3-10      | SM                    | No                    | G1                  | TEM       | No                   |
| Ghassami et al[26] | F   | 53  | 6      | 2-3       | SM                    | No                    | G1                  | NA        | Yes                  |

APR: Abdominoperineal resection; AR: Anterior resection; ESMR-L: Endoscopic submucosal resection with a ligation device; EMR: Endoscopic mucosal resection; TEM: Transmission electron microscope; SM: Submucosa; M3: Mina muscularismucosa.
mations includes symptomatic treatment, surgical resection or other surgical interventions. However, no clinical symptoms can be observed in this patient, and follow-up observations can be continued. Conversely, both the patient and her daughter were diagnosed with scoliosis during childhood, which supported the possibility of heredity. Scoliosis is a common clinical manifestation of NF-1, with 10%-33% of children simultaneously diagnosed with NF-1 and scoliosis [31]. The incidence of scoliosis in adult patients with NF-1 has been reported to be between 10%-77% [32]. The pathogenesis of NF-1-associated spinal deformity is not yet clear and may encompass several factors, including the direct erosion of neurofibroma, dural dilatation of the spinal canal, osteoporosis, precocious puberty, and mesoderm dysplasia [33,34]. Patients with scoliosis may also develop lung damage as time progresses. Surgical correction of NF-1-related spinal deformities may improve the clinical curative effect.

In summary, this case suggests that an NF-1 diagnosis may be complicated by multiple system diseases. The clinical symptoms are complex, non-specific, and not easily identified. We thus need to develop individualized treatment based on the different symptoms of NF-1 patients. Although surgical and symptomatic treatments are currently preferred for multiple rectal neuroendocrine tumors, patients often require multi-system and multi-disciplinary comprehensive treatment. It is necessary to formulate the most appropriate intervention based on individual complications, with the comprehensive application of various technologies and inspection methods, in order to reduce the psychological burden on patients and improve overall quality of life.

ARTICLE HIGHLIGHTS

Case characteristics
A 39 year old woman was admitted to our department because of intermittent bloody stools. The diagnosis was confirmed to be neurofibromatosis type 1 (NF-1) with multiple rectal neuroendocrine neoplasms, vascular malformations and scoliosis.

Clinical diagnosis
A female woman had a primary symptom of intermittent hematochezia without vomiting, abdominal pain, diarrhea, skin flushes, etc.

Differential diagnosis
There were three different diagnoses considered: hemorrhoids, rectal polyps and colorectal cancer.

Laboratory diagnosis
Blood examination showed the hemoglobin levels of the patient was 101 g/L, without other abnormalities such as liver and renal function, tumor markers, etc.

Imaging diagnosis
Computed tomography and magnetic resonance imaging of the chest revealed enlarged mediastinal lymph nodes, dermatoglyphic nodules with long T1 and T2 values, uniform density, clear boundaries and diameters of < 10 mm. A pelvic MRI detected segmental thickening of the right external iliac vein. The middle and lower rectal mucosae were irregularly thickened, with 26.5 mm at the widest point and an irregular signal with long T1 and slightly longer T2 values.

Pathological diagnosis
Pulmonary histological and immunohistochemical examinations showed that neuroendocrine tumor cells were present in the lesions and mutually linked to form cord, nest or gland-like structures. The tumor cells were round, oval or columnar, of varying sizes, with round nuclei, and without obvious mitoses. Cells were CD117 (+), CD56 (+), CK (+), CgA (+), Syn (+), and TTF-1 (+), with a Ki-67 index of < 2%. The subepithelial nerve fibers were in a disordered arrangement, and the cells were elongated, spindle-shaped and oddly distributed in the light-stained collagen matrix. Immune staining revealed CD34 (+) and S-100 (+) expression, deep and S-shaped nuclei, and scattered mast cells.

Treatment
Surgical intervention was advised, however the patient rejected surgery and favored surveillance by regular follow-ups every 3-6 mo.

Related reports
Neuroendocrine tumors are commonly found in the duodenum and pancreas, and rare cases of NF-1-associated multiple rectal neuroendocrine tumors have been reported. We have summarized the relevant literature in the last 20 years and found that only one case, combined with NF-1 in 14 cases, reports of rectal multiple neuroendocrine tumors. In addition, this is the first case where NF-1 is complicated by abdominal iliac vein malformation.

Term explanation
Rectal neuroendocrine neoplasms (NENs) are often derived from peptidergic neurons and neuroendocrine cells of the rectal mucosal epithelium, and are often divided into functional and non-functional types. Non-functional NENs have no specific clinical symptoms. Imaging, endoscopic ultrasound and biopsy are used as the main diagnostic methods for non-functional NENs.

Experiences and lessons
NF-1 diagnosis may be complicated by multiple system diseases. The clinical symptoms are complex, non-specific, and not easily identified. We need to develop individualized treatment based on the different symptoms of NF-1 patients. Although surgical and symptomatic treatments are currently preferred for multiple rectal neuroendocrine tumors, patients often require multi-system and multi-disciplinary comprehensive treatment.

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