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REVIEW ARTICLE

Fibroblastic reticular cell sarcoma of the small intestine: a very rare case report and clinicopathological diagnosis

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Abstract

A 54-year-old man was admitted for the evaluation of fever and abodominal pain. Radiological and endoscopic examination revealed a lung nodule and multiple small intestine uclers. Clinical diagnosis such as tuberculosis and Crohn's disease had been proposed. He developed intestine perforation after small bowel endoscopic procedure. During emergent surgery the involved intestinal segments were resected and a pathological diagnosis of fibroblastic histiocytic sarcoma (FBRC) was made. The patient died in the sixth month after the operation. The management of this cases highlighted the drawback of pattern recognition as the most commonly used clinical reasoning method, and the importance of histological investigation.

Key words: fibroblastic histiocytic sarcoma; tuberculosis; Crohn's disease; small bowel endoscopy; pattern recognition

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A 54-year-old man was referred to our hospital because of abdominal pain and fever. According to the principle of Occam's Razor, we needed to find an inflammatory or neoplastic etiology to explain both symptoms. The patient had been healthy until 3 months before admission. He had intermittent colic around the umbilicus with exacerbation after eating. The patient rated his pain 6–10 on a 10-point scale. The pain did not radiate, was not related to position, and did not improve with the use of a proton-pump inhibitor. A low-grade fever occurred 4 weeks prior to admission. He had night sweats and a 15-kg weight loss. He did not experience cough, chills, melena, hematochezia, vomiting, dysphagia, or altered bowel habits. Pulmonary tuberculosis was diagnosed in the patient 25 years before and resolved after therapy. He had a 45-year history of smoking a pack of cigarettes a day and on average consumed 50 g of alcohol per day for the last 20 years.

On examination, the patient looked chronically ill and cachectic but alert and oriented. His temperature was 38.0°C, his heart rate was 92 beats per min, his respiratory rate was 18 breaths per min, his blood pressure was 106/70 mmHg, and his oxygen saturation was 95 percent while he was breathing ambient air. His weight was 48 kg, and his height was 1.72 m. No lymphadenopathy, icterus, spider angioma, or liver palm was present. The oropharynx was clear. The patient's neck was supple without bruits or goiter. Cardiac examination was normal. His lungs were normal except for decreased breath sounds from both sides. The abdomen was scaphoid without subcutaneous varicose veins. Bowel sounds were normal, and shift dullness was negative. On palpation, the abdomen was soft with tenderness in the left upper and right lower quadrant. No rebound, rigidity, or organomegaly was revealed. Rectal examination revealed no mass. A stool sample was positive for occult blood. He had no peripheral edema. His neurological examination was normal.

Laboratory studies revealed a white cell count of 9200 per cubic millimeter, with 67 percent neutrophils, a platelet count of 337,000 per cubic millimeter, and a hematocrit of 30 percent, with a mean corpuscular volume of 79 μm3. Electrolytes, liver function tests, amylase,

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and coagulation were normal, except for a serum albumin concentration of 3.2 g per deciliter. Urinalysis was normal. His erythrocyte sedimentation rate was 103 mm per hour. Tests of blood cultures, interferon gamma release assay, serum deoxyribonucleic acid for cytomegalovirus, antinuclear antibody, and anti-neutrophil cytoplasm antibody were all negative. A chest radiograph was consistent with chronic obstructive lung disease and resolved tuberculosis.

A gastroduodenoscopy and a colonoscopy with terminal ileal intubation were performed, but they did not reveal any remarkable abnormalities. An air-barium double contrast examination of the small bowel showed multiple ulcers in the jejunum and ileum between normal mucosa (Fig. 1a). Computed tomography (CT) enterography showed skip lesions in the small intestine, including segmental thickening of the bowel wall, marked mucosal enhancement, and lymphadenopathy (Fig. 1b). A CT scan of the lungs incidentally identified a 3.0 × 2.2 cm nodule in the left lower lung with a vessel within it, as well as resolved tuberculosis (Fig. 1c and 1d). Capsule endoscopy was ordered and illustrated large ulcers in the jejunum and ileum with normal mucosa between two lesions (Fig. 1e).

The lung CT findings were not very clear. The location of the nodule explains why it was overlooked on radiograph. The smooth margin of the nodule and the lack of satellite lesions were incompatible with pulmonary tuberculosis. Given the patient's age, the size of the nodule, and the history of heavy smoking, lung cancer should never be excluded. The diffuse involvement of the small bowel, however, cannot be readily explained by lung cancer, because gastrointestinal metastasis of lung cancer is rare. According to a series of case reports, gastrointestinal metastasis usually occurs in the end stages of widely metastatic disease and typically presents with bowel obstruction, massive hemorrhage, and perforation. Although normal ileocecum is infrequent in Crohn's disease, it was a strong differential diagnosis, particularly considering the skip lesions in the small bowel. Among the extra-intestinal manifestations of Crohn's disease, lung involvement is uncommon. However, literature of such manifestations is accumulating and includes drug-related pathologies, airway disease, fistulas, granulomatous disorders, and autoimmune and thromboembolic events. Therefore, the nodule could have theoretically developed in the background of established Crohn's disease.

A pulmonologist saw the patient and agreed that the nodule was inconsistent with tuberculosis. However, he could not relate the pulmonary findings to the small bowel abnormality. The results of microbiological investigations of an induced sputum sample were negative, including Gram stain and acid-fast staining and culture. A bronchoscopy was performed, and the bronchus was patent. A blind biopsy was obtained and revealed unspecific inflammation. The interventionist declined to perform a needle aspiration of the nodule given the risk of hemorrhage. Surgical resection was also considered risky in light of the patient's impaired lung function and poor general status. Double-balloon enteroscopy revealed a large and deep ulcer in the upper jejunum (Fig. 1f). A biopsy was taken. On the next day, the patient complained of abdominal distention, and plain radiography confirmed free subphrenic air. The patient was diagnosed with perforation, and an exploratory laparotomy was performed.

Small intestinal perforation after small bowel enteroscopy is a serious complication in this case, but it was unsurprising. The risk of such an event was relatively high due to the large and deep ulcers in the small intestine. On the other hand, emergency laparotomy undoubtedly put the patient at risk for post-operation complications, but it also provided case management information since surgical resection of the small intestine would lead to a definite histological diagnosis.

During the operation, three ulcerous tumors in the jejunum and ileum were found. The most proximal tumor was perforated, and the other two nearly perforated. Segmental small bowel resections were performed, and a total of 90 cm of the small intestine was removed. The post-operation recovery was complicated by surgical wound infection, but the patient was administered antibiotics and supportive care and did well after all. A pathologist made the final diagnosis of fibroblastic histiocytic sarcoma (FBRC). The patient and his family declined chemotherapy and chose traditional Chinese medicine instead. On follow-up, he developed hemoptysis, fever, and an abdominal mass in the fourth month after discharge and died two months later.

The pathological examination was described hereafter. About 90 cm of the small intestine was sent to the pathology department for gross examination, and three tumors involving all layers of the intestine with ulcers were found (Fig. 1g), the largest one of which was perforated. Some swollen lymph nodes were found adjacent to the tumors. Histologically, the tumor cells originated from submucosal tissue and heavily infiltrated surrounding tissue (Fig. 1h). Tumor cells infiltrated into the mucous membrane to form an ulcer and invaded into the serosa with local perforation. The tumor cells were spindle-shaped and oval with prominent nucleoli and many mitotic figures without obvious nuclear anaplasia. Extensive tumor necrosis and mild lymphocyte infiltration among tumor cells were observed (Fig. 1i and 1j). Tumor cells were present in regional lymph nodes (3/16). Immunohistochemically, tumor cells were strongly positive for vimentin (Fig. 1k), CD68 (Fig. 1l), and EGFR (Fig. 1m), There was partial reactivity for AE1/AE3 (Fig. 1n), LCA (leucocyfe common antigen) (Fig. 1o), smooth muscle actin (SMA) (Fig.

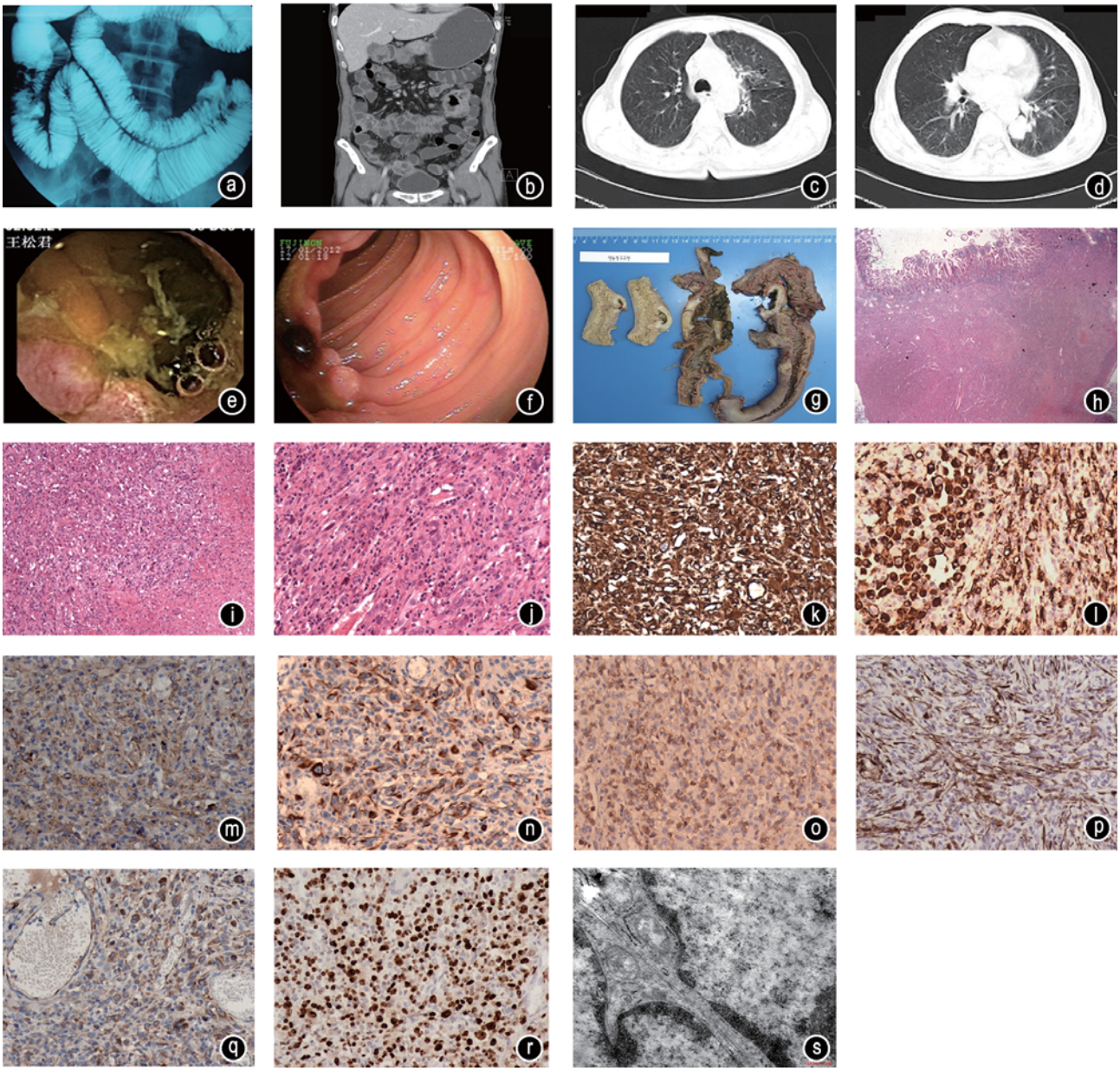

Fig. 1 (a–b) The air-barium and CT enterography showed multiple skip lesions of the small intestine; (c) Old tuberculosis in the left lung; (d) A mass in the left lower lung; (e–f) A large and deep ulcer in the small intestine on capsule endoscopy (e) and small bowel endoscopy (f); (g) Multiple ulcerous tumors in the intestine; (h) The malignancy of submucosal origin and heavy infiltration and invading around tissue (HE staining × 10); (i) Necrosis of the tumor and mild infiltration of lymphocytes (HE staining × 100); (j) Tumor cells with prominent nucleoli and abundant small cytoplasm admixed with lymphocytes (HE staining × 200); (k) Diffuse and strong reactivity for Vimentin (SP × 200); (l) Reactivity for CD68 (SP × 200); (m) Reactivity for EGFR (SP × 200); (n) Partial reactivity for AE1/AE3 (SP × 200); (o) Partial reactivity for LCA (SP × 200); (p) Reactivity for SMA (SP × 200); (q) Reactivity for Desmin (SP × 200); (r) High proportion of Ki-67 expression; (s) Immature desmosomes between tumor cells (electronic microscopy × 17500)

1p), and desmin (Fig. 1q). Tumor cells were negative for CD117, CD34, Dog-1, ALK, CD21, CD35, S100, and CD1a. The Ki-67 tumor index was about 70% (Fig. 1r).

By electron microscope, immature desmosomes were observed (Fig. 1s) between tumor cells; many rough endoplasmic reticulum were present in the cytoplasm of tumor cells.

The pathological diagnosis was FBRC of the small intestine, involving all intestinal layers with metastasis to the regional lymph nodes (3/16).

Discussion

The diagnosis of FBRC relies predominantly on histolytic lineage verification and the exclusion of other poorly

differentiated malignancies by careful histological examination and extensive immunophenotypic investigation [1–5]. Morphologically, FBRC can mimic fibroblasts from other origins with similar long slender cytoplasmic processes, and FBRC can have variable myofibroblastic features [1]. Therefore, definite differentiation between the various entities described above using morphology alone is not possible, and immunohistochemical data plays a key role in these diagnoses [5–7]. In the current classification system of tumors of hematopoietic and lymphoid tissues [8], fibroblastic reticular cell sarcoma has been described as a new subtype, based on the expression of CD68, vimentin, SMA, desmin, and AE1/AE3.

Pathologically, the first disease that merited differentiation in this case was a gastrointestinal stromal tumor (GIST), which is the most common mesenchymal tumor in the alimentary system. GISTs are notorious for their highly variable morphologic features, and they can affect the entire digestive tract with the small intestine as a "hotspot". However, tumor cells in this case were negative for CD117, CD34, and Dog-1, which strongly ruled out diagnosis of this disease. Another possible disease was poorly differentiated carcinosarcoma, and the partial reactivity for AE1/AE3 was suggestive of this possibility, but the origin from the submucosal layer and the positive immunochemical stains with vimentin, SMA, desmin, and CD68 ruled out this malignancy. The immunohistochemical data also helped to exclude other competing diagnoses, such as myofibroblastic tumor, follicular dendritic cell sarcoma, Langerhan's histocytosis, and interdigitating dendritic cell sarcoma. In summary, no malignancy other than FBRC stains positively for SMA, desmin, CD68, and LCA concurrently, as in this case. The electron microscope findings of granular endoplasmic reticulum and underdeveloped desmosomes also support this diagnosis.

Although FBRC tumors are rare, we believe that this case helps to illustrate two important points that apply to general clinical reasoning. First, physicians, especially senior physicians, often employ "pattern recognition" to make a rapid diagnosis. The philosophy of such an approach is that with knowledge and experience, clinicians can form combinations of relevant clinical scenarios (patterns) in their minds that in turn enable each new case to be rapidly evaluated and classified according to its resemblance to existing patterns. To use a metaphor: "If something looks like a duck, walks like a duck, and sounds like a duck, then it is a duck." Although pattern recognition works effectively and efficiently for most problems in daily practice, particularly when quick decision-making is mandatory, such as in an emergency room, it is not immune to cognitive bias and wrong judgments. Furthermore, if physicians anchor to their first impression and refuse adjustment when required, misdiagnosis and errors easily ensue. As for this case, the patient definitely was previously diagnosed with tuberculosis and presented with low fever, night sweats, and weight loss. Therefore, it is quite natural to suspect active abdominal tuberculosis. However, the following diagnostic findings gradually made that diagnosis less likely. On the other hand, when multiple skipping ulcers of the small bowel were found with normal intestinal tissue between them, it was tempting to consider Crohn's disease instead. The nodule in the lungs could also be explained, at least theoretically, by this hypothesis. However, upon thorough consideration, we found many clues that argued against that diagnosis. First, the patient had a rather short clinical course, but he was remarkably wasting. That is not typically seen in Crohn's disease. Secondly, on CT scans, the small intestine was dilated in the first jejunum lesion, while Crohn's disease usually causes strictures of the small intestine. Thirdly, on colonoscopy, the ileocecum, the most common site of Crohn's disease, was normal. To summarize, this case highlights the essential nature of comprehensive evaluation and balanced reasoning of all the relevant data to make good clinical decisions. Even if the clinical scenario seemingly fits a certain diagnosis, rather than jumping to the conclusion, one still needs to arrange necessary diagnostic workups and carefully rule out other competing diagnoses.

The second point of this case is the importance of histological investigation. "Tissue is the issue", and the truth and profundity of this adage can never be overstated. After all other approaches failed to lead to a definite diagnosis, we were left with no choice but to employ enteroscopy to investigate the small intestine. Enteroscopy brought certain risks and resulted in the serious complication of perforation. However, it was perforation that justified emergent laparotomy and led to the eventual pathological diagnosis. Without such an intervention, the patient could have gone undiagnosed for additional time. We also believe that the dramatic course of this case has served to reflect the spirit of Chinese philosophy. According to ancient Chinese thinkers, the natural law governing the universe is a law of cyclic development, and things that develop to one extreme are bound to tend toward the opposite. In other words, nothing is fixed forever. Looking at the perforation from this perspective, we realize that it is a two-fold story. On one hand, perforation is undoubtedly a serious complication and an adverse event, but on the other hand, it also helped to finally diagnose this case. We learned to watch out and take care even in favorable clinical situations and stand resolutely in hard ones. In other words, physicians should withstand adversities in clinical practice, always support their patients, and hope for the best.

Unfortunately, the patient declined post-operative chemotherapy and died shortly thereafter, despite all the

efforts. The natural course of this case was consistent with the highly aggressive behavior of FBRC. Based on his terminal symptoms, we speculated that the pulmonary lesion was probably a metastatic lesion of the disease, and the intra-abdominal tumor had recurred.

Tumors derived from reticular cells are uncommon, and those of FBRC origin are even rarer. Turner et al. described the first well-established case of FBRC in 1984 [2]. In 1998, Andriko *et al* published a report on 11 patients with lymph node reticular cell neoplasms, including 3 cases of FBRC origin [3]. Since then, less than 20 cases of FBRC have been reported that involve lymph nodes, spleen, and liver [4–7, 9, 10]. Although the rarity of FBRC neoplasms has largely prevented a full appreciation of their biological behavior, extranodal presentation is frequent, and the clinical course is generally aggressive in patients with FBRC malignancies. Evidence of FBRC management is scarce. Surgical debulking is the primary treatment option, but the roles of chemotherapy and radiotherapy are unproven. To the best of our knowledge, this is the first case of FBRC sarcoma of the small intestine with a probable lung origin.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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