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Case Report
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Multisystem Inflammatory Syndrome Associated with Gastrointestinal Bleeding and Pancytopenia in a Child with Systemic Multiple Tuberculosis Infection: A Case Report

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Case Presentation

We report the case of a 16-year-old boy with tuberculosis-associated childhood Multisystem Inflammatory Syndrome (MIS). The child presented with systemic multisite tuberculosis: Pulmonary Tuberculosis, Intestinal Tuberculosis, Tuberculous Peritonitis (PT-IT-TP); He had severe GI bleeding, incomplete ileus, profound anemia, pancytopenia, extreme emaciation, severe hypoalbuminemia. His initial symptom was "abdominal pain". The patient had intermittent right lower quadrant pain in June 2021 without any inducement, which could be relieved on his own, and he did not go to the hospital to see a doctor (2022-01). The patient had occasional diarrhea, up to 3 to 4 yellow loose stools per day, abdominal pain relieved after defecation, no mucus, pus and blood in the stool, no fever, night sweats, vomiting, coughing, etc. When the symptoms of diarrhea are obvious, the parents of the children give the children "montmorillonite powder orally" by themselves, and the diarrhea can be relieved (2022-01-07). I saw a doctor at the local county hospital and underwent a colonoscopy: Multiple ulcers in the colon, possible Crohn's disease; pathology: Chronic inflammation of the colonic mucosa (Colonoscopy pictures) (Figure 1). From April 2022, the frequency of diarrhea increased compared with before, and the stool was dark brown, accompanied by night sweats, occasional cough, and shortness of breath after activity. From April 2022 to June 2022, the patient lost 10 kg in weight within 2 months. The patient received no special treatment before visiting our hospital. On June 6th, 2022, I went to see a doctor in our hospital. Laboratory tests showed: Hb 34 g/L, albumin 20 g/L. Chest CT scan (Figure 2): Multiple nodules with partial cavities in both lungs (maximum cavity 51 × 30 mm), Abdominal and pelvic CT display (Figure 3): Both abdominal cavity and pelvic cavity have effusion, multiple nodules with partial calcification, gallbladder stones, double kidney stones. The patient was admitted to the Pediatric Intensive Care Unit (ICU) with "dyspnea with severe anemia."

After being admitted to the hospital, he underwent further examinations, including blood mNGS, sputum mNGS, and feces mNGS to detect the nucleic acid sequence of *Mycobacterium tuberculosis* (Table 1). Blood T-SPOT.TB positive. Higher concentrations of systemic inflammatory markers: Including hypersensitive C-Reactive Protein (hs-CRP), Procalcitonin (PCT), Serum Amyloid A (SAA,), and Stool Calprotectin (SC), Left shift in white blood cell count and massive decrease in lymphocytes were also found (Table 2). On hospital day 1, he had a higher concentration

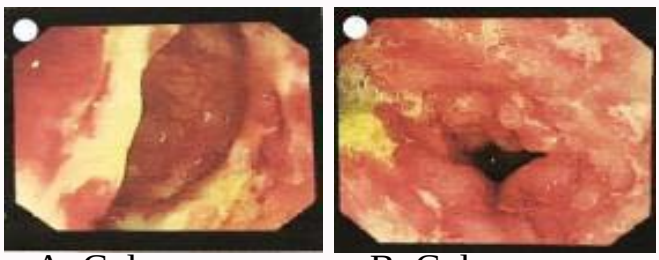

Figure 1: Colonoscopy.
Colonoscopy A, shows the ileocecal part with congestion and edema, nodular and uneven mucosa, irregular ulcers, and white coating attached.
Colonoscopy B, shows the sigmoid colon, which is obviously congested and edematous, with irregular ulcers, the bottom is covered with white fur, and varies in size. There is no obvious "worm chisel"-like change around the ulcer.

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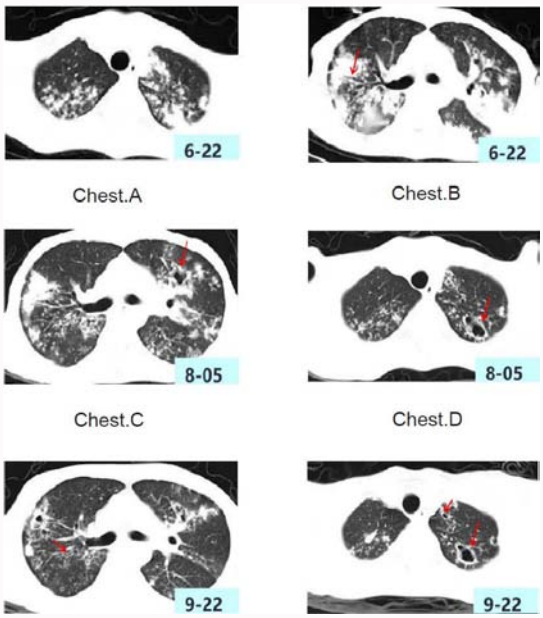

Figure 2: Chest CT scan.
Chest A (transverse section): Small nodules are unevenly distributed in the upper lobes of both lungs, and the nodules are of varying sizes. The edge may be blurred, with the sharp posterior segment as the leading edge. Chest B (transverse section): In the exudative stage of tuberculosis, there are flake-like dense shadows in the lung parenchyma with unclear boundaries and air bronchial signs (red arrows).
Chest C (transverse section): Nodular and patchy high-density lesions can be seen in both lungs, and cavitary. Chest D (transverse section): Nodules distributed unevenly in the apex of both lungs. A cavity wall is seen in the posterior segment of the apex of the upper lobe of the left lung, and the inner wall may be irregular (red arrow).
Chest E (transverse section): The lesions can spread along the bronchus, forming signs of bronchial dissemination, and bronchial wall thickening and stiffness can be seen (red arrow).
Chest F (transverse section): Multiple cavities of varying sizes and wall thicknesses are seen in the upper lobe of the left lung (red arrow).

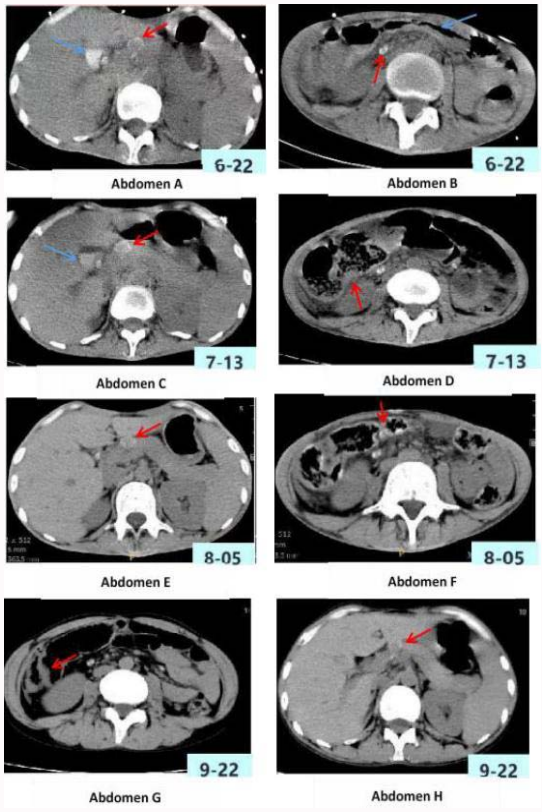

Figure 3: Abdomen CT scan.
Abdomen A (abdominal transverse axis): Nodular high-density lesions (blue arrow) can be seen in the left lobe of the liver, and high-density calcification lesions (red arrow) are found in the pancreatic Neck.
Abdomen B (abdominal transverse axis): Transverse colon wall thickening (blue arrow), retroperitoneal lymph node calcification (red arrow).
Abdomen C (abdominal transverse axis): Nodular high-density lesions (blue arrow) can be seen in the left lobe of the liver, and high-density calcification lesions (red arrow) can be seen in the pancreatic neck.
Abdomen D (abdominal transverse axis): Abdominal gastroenteritis, intestinal wall thickening in the colon and liver area (red arrow).
Abdomen E (abdominal transverse axis): High-density calcifications (red arrow) are seen in the pancreatic neck.
Abdomen F (abdominal transverse axis): The transverse colon wall is thickened and dense (red arrow).
Abdomen G (abdominal transverse axis): The wall of the ascending colon is thickened (red arrow).
Abdomen H (abdominal transverse axis): High-density calcifications (red arrow) are seen in the pancreatic neck.

of N-Terminal Brain Natriuretic Peptide (NT-proBNP), a marker of cardiac injury, NT-proBNP was 1652 pg/mL (normal range <300 pg/mL), Echocardiography showed: A small amount of fluid in the pericardial cavity, LVEF 62%.

The patient was given total parenteral nutrition after admission due to severe gastrointestinal bleeding (on the 9th day of hospitalization, the patient's stool color turned brown, abdominal pain improved, Hb was 93 g/L, the gastric tube was removed, and the diet was gradually allowed).

(Blood Rt line chart) (Figure 4) Isoniazid 0.3 g qd po (for 6 months) and rifampin 0.45 g qd po (for 6 months) were given on the first day of admission; Intravenous drugs include: Levofloxacin 0.5 g qd (for 31 days), amikacin 0.5 g qd (for 60 days), meropenem 1 g q8h for anti-infection (for 11 days). Other treatments include IV albumin 30 g qd (2 days), thymosin 20 mg QD subcutaneously (for 7 days), Oral Ansu configuration solution (55.8 g Ansu powder + 200 ml warm water, configured into 250 ml Ansu solution (for 65 days), Likejun 20 mg orally TID (for 5 days) with 3 Red Blood Cell (RBC) infusions (200 ml per infusion). 2022-6-22 After 16 days of treatment, the CT of the chest, abdomen and pelvis showed (Figure 3); The lung, abdominal cavity, and pelvic lesions did not improve compared with before, and his clinical condition did not improve significantly. Pyrazinamide 1 g qd po was added (for 6 months). Over the next 6 weeks, he showed slow but continuous improvement in each system. On the 60th day of admission, his body weight increased by 2 kg from the time of admission, his symptoms improved, his laboratory tests returned to baseline, and he was discharged (home oral anti-TB drugs). Follow-up after discharge: (2022-09-21) Sputum (*Mycobacterium tuberculosis* culture negative). (2022-09-28) Sputum (*Mycobacterium tuberculosis* culture negative), weight 43 kg (BMI 14.88), Hb 141 g/L. Chest CT (Figure 2): Multiple infections in both lungs with cavities, slightly improved compared to 22-08-05 CT. Contrast-enhanced CT of the abdomen and pelvis showed (Figure 3): Local intestinal wall edema and thickening in the ileocecal region, ascending colon, and transverse colon, and multiple enlarged lymph nodes with calcification in the retroperitoneum, abdominal cavity, and pelvic cavity, Abdominal and pelvic intestinal wall edema improved compared with the previous 22-08-05; (9.22 CT image) 2023-01-12 sputum (*Mycobacterium tuberculosis* culture negative).

Table 1: *Mycobacterium tuberculosis* nucleic acid sequences (mNGS).

Type of inspection	Genus name of bacteria	Relative abundance of bacterial genera (%)	stringent sequence number	Strain name	Relative abundance of bacterial species (%)	strain sequence number	Strict sequence number of bacterial species
Blood	*Mycobacterium tuberculosis* complex	2.64	4	*Mycobacterium bovis*	0.64	1	0
		2.64	4	*Mycobacterium vole*	0.67	1	0
		2.64	4	*Mycobacterium mongoose*	0.67	1	0
		2.64	4	*Mycobacterium tuberculosis*	0.65	1	0
Phlegm	*Mycobacterium tuberculosis* complex	0.01	57	*Mycobacterium africanum*	0	10	0
		0.01	57	*Mycobacterium bovis*	0	5	0
		0.01	57	*Mycobacterium canettii*	0	5	0
		0.01	57	*Mycobacterium capricans*	0	10	0
		0.01	57	*Mycobacterium vole*	0	3	0
Defecate	*Mycobacterium tuberculosis* complex	0.03	878	*Mycobacterium tuberculosis*	0	155	1
		0.03	878	*Mycobacterium africanum*	0	126	0
		0.03	878	*Mycobacterium bovis*	0	121	0
		0.03	878	*Mycobacterium canettii*	0	56	0
		0.03	878	*Mycobacterium capricans*	0	129	0
		0.03	878	Mycobacteria*	0	2	0
		0.03	878	*Mycobacterium vole*	0	130	0
		0.03	878	*Mycobacterium mongoose*	0	115	0
		0.03	878	*Mycobacterium antelope*	0	116	0
		0.03	878	*Mycobacterium pinnipedii*	0	107	0

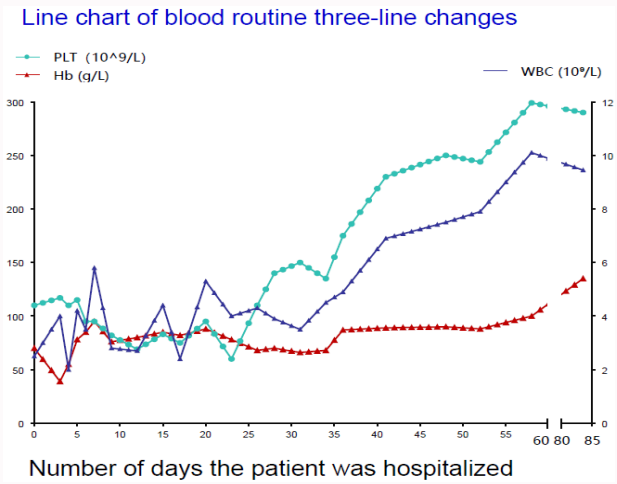

Figure 4: Blood: Line chart of blood routine three-line changes

Table 2: Laboratory results relevant to treatment.

Check date	WBC	Hb	PLT	ESR	hs-CRP
02-06-2022	13.24	73	100	11	38.2
06-06-2022	5.42	70	70	103	82
05-07-2022	2.42	73	109	68	174
05-08-2022	4.31	101	117	42	34.6
22-09-2022	5.03	141	123	50	31

Institutional normal range; WBC: White blood cells (3.84-9.84) × 10^3/μL; Hb: Hemoglobin (11.0-14.5 g/dL); PLT: Platelets (175-332) × 10^3/μL; ESR: Erythrocyte Sedimentation Rate (0-15 mm/h); hs-CRP: Hypersensitive C-Reactive Protein (<8 mg/L)

Discussion

The patient's performance met the criteria for the inflammatory phenotype of a systemic multiple tuberculosis infection case: He had organ damage in at least 4 organ systems, lung, intestinal tract, pancytopenia, heart damage: A small amount of fluid in the pericardial cavity, he was hospitalized on day 1, the peak value of NT-proBNP was 1652 pg/mL. The GI bleeding reported here is especially unusual in a pediatric patient with tuberculosis because it is difficult to differentiate from "Crohn's disease." The peak incidence of Crohn's disease in China is between the ages of 15 and 25. The main symptoms are: abdominal pain, diarrhea, and weight loss. It is a chronic inflammatory granulomatous disease of the digestive tract with unknown etiology. It has chronic inflammation from the mouth to the anus, the most obvious lesions in the ascending colon [1]. Jump ulcers and transmural inflammation throughout the GI tract are characteristic of Crohn's disease, whereas peritoneal inflammation in Crohn's disease has rarely been reported [2]. The patient underwent a Multidisciplinary Case Discussion (MDT): Colonoscopic biopsy in an outer hospital showed no obvious damage to the ascending colon. Mesenteric artery CTA and vein CTV: No abnormalities were found, no oral ulcers and joint swelling and pain in the past. Abdominal and pelvic CT in our hospital showed no thickening of the wall of the ascending colon, and obvious calcified nodules in the peritoneum. Combined with the decrease in inflammatory indicators after anti-tuberculosis treatment, according to the explanation of disease monism, considering intestinal tuberculosis, Crohn's disease is less likely. The patient's 2020 physical examination found no abnormal organs, and his heart function, lungs, gastroscopy, and colonoscopy were all normal. The extent of gastrointestinal bleeding in our patient

was similar to that observed in adults with systemic tuberculosis [3,4]. The site of gastrointestinal bleeding is not clear. This severe gastrointestinal bleeding is linked to an increased risk of death [5].

Cases of systemic multiple tuberculosis infection associated with severe gastrointestinal bleeding and pancytopenia raise concerns in severe tuberculosis cases in adults [6]. To the best of our knowledge, this is the first report of evidence of multiple organ dysfunction in adolescents with PT-IT-TP and pancytopenia. Evidence for this dysfunction was unexpected. After MDT discussion, the patient and parents actively participated in the clinical decision-making process, and decided to treat the boy with three anti-tuberculosis drugs at the same time for 6 months (isoniazid 0.3 g, once a day; rifampicin 0.45 g, once a day; pyrazinamide 1 g, Once a day). Intravenous drugs include: Levofloxacin 0.5 g qd (for 31 days; On the 31st day of levofloxacin intravenous injection, the patient had 2 epileptic seizures, and no obvious abnormalities were found in video EEG, blood gas, blood sugar, and head MR+FLAIR+DWI. MDT team neurologist consideration: Levofloxacin side effects, discontinue levofloxacin), Amikacin 0.5 g qd (for 60 days). This decision was based on systemic inflammatory markers, lung and abdominal CT scans, which we planned to perform monthly after treatment initiation, and a comprehensive clinical examination assessment and comprehensive evaluation of lung and other organ function.

Assessing PT-IT-TP in children and adolescents is particularly challenging and requires pediatricians, specialists experienced in managing tuberculosis (including gastroenterologists, hematologists, respiratory physicians, cardiologists, radiologists, and immunologists) home) and international experts. Intestinal *M. tuberculosis* infection results in inflammation and lesions that form ulcers, fistulas, or strictures. Gastrointestinal bleeding from intestinal tuberculosis can be due to several reasons: Ruptured ulcers, damaged blood vessels, inflammation and tissue damage, formation of necrotic tissue [7].

Symptoms of tuberculous peritonitis in children may vary from individual to individual, but common symptoms may include: Abdominal pain, which may be constant or intermittent, abdominal distension or mass, fever, nausea, vomiting, weight loss, ascites (peritoneal accumulated liquid). Imaging tests, such as X-rays, CT scans, ultrasound, etc., to identify abdominal lesions. Tuberculous peritonitis in children can lead to peritoneal, pelvic, and pericardial effusions, the following are possible causes and mechanisms [7]: Inflammation and infection can result in an inflammatory exudate from the peritoneal surface, which may accumulate in the abdominal and pelvic effusions, peritoneal and pelvic effusions may communicate with the thorax through the diaphragm and the upper border of the peritoneal cavity, resulting in fluid communication between the pleural and pericardial cavities, which may lead to pericardial effusion [8].

Childhood tuberculosis and pancytopenia may be the result of a combination of factors and mechanisms, the following are some possible causes [9]: Bone marrow damage: *Mycobacterium tuberculosis* infection may cause inflammation of the bone marrow, interfering with normal hematopoiesis. Malnutrition: TB can cause loss of appetite, poor digestion and absorption, and weight loss, which can affect the body's absorption and utilization of nutrients, which can affect the production of red and other blood cells. Tuberculosis can interfere with the normal function of the immune system, causing abnormal effects on the body's production of blood-forming cells. It should be emphasized that tuberculosis in children can be heterogeneous, affecting multiple organ systems. If a child develops systemic multisite tuberculosis with pancytopenia, this may be a serious condition.

We urge clinicians and policy makers not to underestimate the mortality risks and consequences of gastrointestinal bleeding and pancytopenia in children with systemic multiple tuberculosis infection. We also call for urgent research to inform treatment and improve outcomes in children with systemic multiple tuberculosis infection. More data are urgently needed to identify risk factors for targeted prevention and support.

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