CASE REPORT

A rare presentation of Hodgkin's lymphoma in a very young child, with involvement of the appendix

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SUMMARY

Hodgkin's lymphoma involving the appendix in young children is an exceptionally rare disease. We report a case of a child less than 3 years who presented to us with gradual weight loss, progressive pallor and diffuse abdominal pain. The symptoms were preceded by a history of varicella infection about 6 months ago. The clinical progression was marked by intermittent episodes of acute abdominal pain and fever, mimicking acute intra-abdominal inflammatory process such as appendicitis. Investigations revealed that the child had direct Coomb's test positive haemolytic anaemia, raised platelet counts, lymphopenia and hypergammaglobulinaemia. The CT of the abdomen showed the presence of significant lymph nodes. Abdominal laparoscopy and biopsy of the lymph nodes showed mixed cellularity Hodgkin's lymphoma that also involved the appendix. Subsequent staging detected an advanced stage IV disease. The child was referred immediately to a specialised oncology centre for further management. Unfortunately he was lost in follow-up.

BACKGROUND

The diagnosis of Hodgkin's lymphoma in young children is uncommon.^{1–3} Hodgkin's lymphoma involving appendix is rare. Primary appendicular lymphoma is even rarer (0.015%) across different age groups. There are isolated reports of appendicular non-Hodgkin's lymphoma and Burkitt's lymphoma in children. Even in adult literature studies there are very few reports of cases of Hodgkin's disease involving the appendix.

The case that we are reporting is of a very young child. The clinical presentation had suggested a chronic inflammatory or possible malignant pathology. Many of the investigation findings were associated clues to our eventual diagnosis of Hodgkin's lymphoma. However, there were no significant organomegaly or enlarged accessible lymph nodes. CT of the abdomen had revealed presence of significant intra-abdominal lymph nodes located adjacent to vital intra-abdominal structures. Hence we had to perform laparoscopy of the abdomen to take lymph node biopsy and rule out lymphoreticular malignancy. During the laparoscopy we found that the appendix was very difficult to locate and isolate. It was embedded in a large mass adherent to the adjacent structures around it. The tissue biopsy from the enlarged lymph nodes as well as the appendicular mass revealed the presence of Hodgkin's disease involving the appendix. Almost all the symptoms and signs of this child (including the presence of partial villous atrophy in duodenal

biopsy) were explained in retrospect from our final diagnosis. Our final diagnosis could have been missed had we not undertaken the risky decision to perform laparoscopic biopsy of the tissues involved. We took the decision solely on the basis of a strong clinical suspicion, though there was no obvious lymphadenopathy on external examination.

Our extensive search of contemporary English literature did not reveal a single case of paediatric Hodgkin's lymphoma involving the appendix. The very young age of presentation and a very unlikely location (appendix) make this a very rare case worth reporting.

CASE PRESENTATION

A 2-year 10-month-old child had presented with gradual onset of systemic symptoms over a period of 6–8 months. These included weight loss, pallor, intermittent fever and recurrent abdominal pain. The child had an episode of fever and skin rash, which was diagnosed as varicella infection, when he was about 2 years old. Following that illness, the child was having lack of appetite and poor weight gain. There were multiple episodes of febrile illness along with abdominal pain during this period. Some of these were associated with diarrhoea and intermittent vomiting. These prompted the parents to seek medical advice on a number of occasions before the boy was actually referred to us.

The child was born at term. He was the first born of non-consanguineous parents. He had received all routine immunisations. However, he was not given the varicella vaccine. His developmental milestones were normal before he became ill. His growth parameters were between the 10th and 50th centile for his age until the age of 2 years. Subsequently, he had poor growth and it fell below the third centile when he was referred to us.

Even before his referral, the child was extensively investigated for his symptoms, in particular the failure to thrive. Although there were histories of recurrent febrile episodes, none of these were labelled as significant infection. Apart from the incidental detection of villous atrophy with possible giardiasis, nothing significant was diagnosed.

INVESTIGATIONS

A review of the series of investigations before his referral to us, revealed gradually progressive anaemia (haemoglobin (Hb) 68 g/L), recent onset relative depletion of lymphocytes in blood (ALC ~ 1000), increasing platelet count ($600 \times 10^9/L$), normal Hb electrophoresis and hypergammaglobulinaemia (1803 mg/dL; normal less than 700 mg/dL).

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The blood cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies, vitamin B₁₂, folic acid and total complement level were normal and serology for blood-borne infections (hepatitis B, hepatitis C and HIV) were negative. There was negative purified protein derivative tuberculin test (STU). Chest X-ray was also normal. The anti-tissue transglutaminase and antiendomysial antibodies were negative. Endoscopic duodenal biopsy revealed subtotal villous atrophy with crypt hyperplasia, showing *Giardia* and *Isospora* cysts.

Our institute investigations showed severe pallor (72 g/L), Coombs' positive haemolytic anaemia, high lactate dehydrogenase level (1632 U/L; normal less than 550), absolute lymphopenia (930 cell/ μ L), thrombocytosis (660×10^9 /L), high erythrocyte sedimentation rate (70 in first hour.) and a high C reactive protein level (78.2 mg/L; normal less than 5 mg/L). Liver function tests, serum electrolytes, amylase, lipase and the coagulation profile were all normal and tests for infectious agents such as malaria, typhoid and dengue came out negative. Metabolic screening and blood culture reports were negative as well. Ultrasound-guided abdomen revealed abdominal lymph nodes, which in contrast-enhanced CT of the abdomen could be localised in the retroperitoneal and porta-hepatis regions (figure 1) as non-enhancing soft tissue masses (figure 2). Laparoscopic biopsy of the nodes was undertaken, which on histological sections showed mixed cellularity-type Hodgkin's lymphoma. An inflamed hugely distended appendicular mass was removed as well, which showed similar histological picture. The specimens (lymph node and the appendix) showed CD15, CD30 positivity in neoplastic Reed-Sternberg cells and leucocyte common antigen (CD45) and CD20 positivity in background cells,

consistent with mixed cellularity diagnosis. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan (figure 3) showed focal uptake of the tracer in supraclavicular, subcarinal, retroperitoneal area and liver, making this a stage IV disease, at presentation.

DIFFERENTIAL DIAGNOSIS

In the presence of failure to thrive progressive pallor and abdominal lymphadenopathy, chronic infectious aetiologies such as tuberculosis, HIV, Epstein-Barr virus infection were strongly considered. However, these were excluded on the basis of prior vaccination status, absence of any sick contact, negative tuberculin test, negative HIV serology and lymphocyte count/morphology. Inflammatory conditions such as celiac disease with abdominal lymphadenopathy seemed unlikely, on the basis of negative tissue transglutaminase and antiendomysial antibodies with negative gluten challenge test, even though the duodenal biopsy showed villous atrophy. Inherited immunodeficiency states such as common variable immunodeficiency (CVID) could have been a possibility with failure to thrive, autoimmune haemolytic anaemia, intestinal parasite infestation and intra-abdominal lymphadenopathy. However, hypergammaglobulinaemia, absence of chronic diarrhoea and cervical lymphadenopathy were all against it. Lymph proliferative conditions such as Castleman disease, Rosai-dorfman, autoimmune lymphoproliferative syndrome share common features of thrombocytosis, hypergammaglobulinaemia and Coombs' positive haemolytic anaemia. However, they have predominant cervical lymph nodes and lymphocytosis in peripheral blood smear.

CECT Abdomen → Non-enhancing soft tissue lesions seen in retroperitoneum & portahepatis region.
The portal vein appears compressed → by Lymphadenopathy

Figure 1 Contrast-enhanced CT of the abdomen showing retroperitoneal soft tissue mass.

Figure 2 Contrast-enhanced CT of the abdomen showing retroperitoneal mass compressing porta hepatis.

TREATMENT

Review of medical records suggested that the child received symptomatic treatment since he started to have clinical symptoms. These included multiple doses of antibiotics for his fever and intermittent infections. He was extensively investigated for failure to thrive and associated malabsorption. He was treated adequately with antigiardial therapy on the basis of the suspicion of giardiasis contributing to the partial duodenal villous atrophy detected by small intestinal biopsy.

After admission, the child was given packed cell transfusion, for severe anaemia, after proper grouping and cross-matching.

The transfusion was uneventful, despite the presence of auto-antibodies in the patient's serum. Empirical antibiotics were started awaiting blood culture results and supportive measures were taken to control fever, maintain hydration and nutrition. The fever subsided within 2 days but the abdominal pain continued to persist. As part of the diagnostic laparoscopic procedure, the appendix was removed as it was found inflamed and enlarged. The postoperative course was uneventful. The pain in the abdomen subsided. Subsequently, antibiotics were stopped and supportive treatment was continued.

OUTCOME AND FOLLOW-UP

As soon as we received a confirmed diagnosis we discussed it with his parents and immediate family members. As the disease process was already well advanced, we had stressed on the need to start immediate and appropriate chemotherapy. We described the implication and probable prognosis with the family. We immediately referred the child to a specialised paediatric oncology centre for further management. However, unfortunately the child was lost in subsequent follow-up.

DISCUSSION

We describe this case of a very young male child. He had initially presented with gradual weight loss, progressive pallor and diffuse abdominal pain, over a protracted course of 6–8 months. These systemic symptoms had followed an episode of varicella infection. The clinical course was marked by intermittent abdominal pain and fever, often simulating an intra-abdominal inflammatory pathology. The child had positive direct Coombs' test anaemia, raised platelets, decreased lymphocytes and raised γ -globulins in blood tests. There was a possible parasitic infection and recent

Figure 3 Positron emission tomography (PET) scan showing diffuse stage IV Hodgkin's lymphoma.

discovery of intra-abdominal lymph nodes without any cervical and mediastinal lymphadenopathy. Anaemia and fever were partly correctable with antibiotics, red cell transfusion and supportive measures. Subsequent investigations revealed the underlying diagnosis of Hodgkin's disease involving the appendix in this case. The varicella infection which had preceded many of the clinical symptoms in this child might be purely coincidental. Whether he was already suffering from an underlying malignant process during this infection is also debatable.

In studies reported from North America,¹ Europe² and India³ Hodgkin's lymphoma has been found to be rare in children below 3 years. Indian data^{3, 4} from tertiary care centres show a high male to female ratio in these cases. The younger age of presentation was associated with more advanced disease, more constitutional symptoms and predominantly mixed cellularity histological types. In younger group of children with Hodgkin's lymphoma less mediastinal involvement⁵ and more bulky disease were reported compared with that in older children. Some reports⁶ had also suggested greater chances of advanced disease in children older than 8 years.

Large reviews⁷ in 1994 found the risk of varicella zoster to be greatest in Hodgkin's lymphoma compared with other haematological malignancies. This actually confirmed the initial report⁸ of such an association.

Reports of lymphoma affecting the appendix in children are very rare. Matsushita *et al*⁹ reported the first paediatric case of T (Th1)-cell appendicular non-Hodgkin's lymphoma in a 7-year-old child. Subsequently, primary appendicular MALT (mucosa-associated lymphoid tissue) lymphoma in a 6-year-old child was reported.¹⁰ There were also reports of cases of intussusceptions due to non-Hodgkin's lymphoma in children.^{11, 12} Burkitt's lymphoma mimicking appendicitis in children has also been reported.^{13, 14}

Multiple adult case reports^{15–21} had also described various types of lymphoma affecting the appendix. Almost all reported cases of appendicular lymphoma have proved to be non-Hodgkin's lymphoma.²² There are only four adult cases of appendicular Hodgkin's disease reported²³ so far. There have been no reports of Hodgkin's lymphoma of the appendix in very young children.

Learning points

- ▶ Hodgkin's lymphoma is rarely encountered in very young children.
- ▶ Primary involvement of the appendix in such cases has yet to be reported.
- ▶ This presents a diagnostic challenge.
- ▶ Differentiation from other chronic inflammatory and malignant conditions is essential to arrive at an accurate diagnosis.
- ▶ High index of clinical suspicion is required for early diagnosis and appropriate therapy.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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