# Idiopathic Intramural Intestinal Haemorrhage Complicating The Management Of Langerhans Cell Histiocytosis

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### Abstract

A 3 year old girl with heterotaxy was diagnosed to have multisystem Langerhans cell histiocytosis (LCH) based on the typical dendritic cells in a scalp biopsy, positive CD1a and S-100, and multisystem involvement. She was treated with Vinblastine and Prednisolone. The first two weeks of therapy was complicated by mycoplasma pneumonia, respiratory syncytial virus pneumonia, and Clostridium difficile infection. She developed significant GI bleeding and anemia during the fourth week of therapy. A laparotomy was performed, and the procedure revealed extensive duodenum and jejunum intramural haemorrhage. A duodeno-jejunal resection and end-to-end duodeno-jejunal anastomosis were performed. Typical dendritic histiocytes were not found in the resected tissue and the tissue was CD1a negative. Gastrointestinal intramural haematomas have not been previously reported to occur in LCH. Intestinal intramural haemorrhage is a rare entity but occurs in children and is usually related to trauma. The exact aetiology of the duodeno-jejunal intramural haemorrhage in this case remains unexplained. Possible causes include: 1) trauma due to coughing that the patient had during her management; 2) effects of chemotherapy (unlikely since she was not significantly thrombocytopenic); 3) Langerhans cell histiocytosis involving the small intestine (unlikely since the resected tissue were histologically and immunologically negative for LCH); 4) Intrinsic defects in the child's intestines since she was reported to have heterotaxy. This case reports an unusual complication that occurred in a 3 year old girl with LCH.

### INTRODUCTION

We report an unusual case of intramural intestinal haemorrhage in a 3 year old girl who was treated for Langerhans cell histiocytosis. Langerhans cell histiocytosis (LCH) is characterized by abnormal proliferation of dendritic histiocytes in various tissues. Rarely, spontaneous bleeding affecting the central nervous system has been reported [1]. Intramural intestinal haemorrhage is an uncommon event and has been reported to occur following abdominal trauma, factor VIII deficiency and other coagulopathies, endoscopic small bowel biopsy and anticoagulation particularly with warfarin; the former 3 being the more common causes in children[2-8]. However, intramural small intestinal haemorrhage has not been reported to occur in LCH.

## CASE REPORT

A 3 year old female presented with a chronic erythematous maculo-papular rash affecting her torso and scalp. She had right proptosis, right temporal scalp swelling and classical features of diabetes insipidus. Initial imaging revealed a large soft tissue mass with extensive bony destruction of the right skull base, frontal and temporal bones. There was absence of posterior pituitary bright spot on brain magnetic resonance imaging. Abdominal imaging revealed heterotaxy comprising the presence of a midline liver, asplenia and azygous continuation of her inferior vena cava. A diagnosis of multisystem langerhans cell histiocytosis (LCH) was confirmed after scalp biopsy showed the papillary dermis effaced by a mononuclear population of histiocytes with immunohistochemistry positive for CD1a and S-100. Treatment was initiated following the Children's Cancer and Leukemia Group LCH treatment guidelines for group 3 (multisystem &central nervous system risk) disease. Intravenous vinblastine at 6mg/m2 weekly, oral prednisolone 40mg/m2 TID, and 10mg omeprazole daily were commenced. Co-trimoxazole 240mg BID on 2 consecutive days weekly prescribed for Pneumocystis carinii prophylaxis and oral Desmopressin 25 mcg was administered usually twice daily when urine specific gravity dropped below 1.005.

During the first week of chemotherapy, investigations for a pre-existing cough revealed Mycoplasma pneumoniae polymerase chain reaction positivity. A 14 day course of oral clarithromycin was prescribed to treat her pneumonia. During the second week of chemotherapy she was readmitted with febrile neutropenia, Her white cell count was 2.8 x 109/ L ; platelets were 140 x 109 /L. Stools were positive for Clostridium difficile toxin and adenovirus. Intravenous Piperacillin/Tazobactam, Gentamicin, metronidazole, amphotericin B and recombinant Granulocyte colony-stimulating factor were commenced. She was subsequently diagnosed with respiratory syncytial virus (RSV) Pneumonia.

During the fourth week of treatment, 6 days after the 3rd doses of vinblastine and daily prednisolone, she developed tachycardia. Investigations revealed a decrease in haemoglobin from 11.5g/dl to 7.4g/dl and a leucocytosis of 29.6 x109 /L; her platelet count was 480 x 109 /L, and coagulation screen was also normal. There was no obvious source of bleeding noted at this time. Despite adequate administration of blood products, her haemoglobin continued to decrease. Prompted by melena manifesting 3 days later, oesophago-gastroduodenoscopy performed revealed small mucosal erosions with minimal bleeding within the duodenum not in proportion to the amount of blood loss observed clinically. Melena persisted despite a proton pump inhibitor (omeprazole) and octreotide infusions.

The 4th dose of vinblastine had been withheld. One week after the onset of bleeding, week 5 of chemotherapy, she developed vomiting, peritonitis and further significant blood loss. A repeat abdominal computed tomography angiography showed free fluid in her abdomen and revealed features suggestive of duodenal and proximal jejunal haematoma with luminal narrowing (figure 1). A possible localised perforation of the proximal jejunum was also suspected.

### Figure 1

Axial abdominal computed tomography angiography showing a dilated duodenum and Jejunum (a); extraluminal high attenuation representing possible Intramural haematoma (b); Intraluminal contrast suggesting active bleeding into the small intestine (c).



At exploratory laparotomy, haemoperitoneum and a grossly dilated duodenum and proximal jejunum with extensive intramural haemorrhage were found. There were patchy regions of infarction necessitating duodeno-jejunal resection and end to end duodeno-jejunal anastomosis. Decompression of the haematoma in the residual jejunum was then performed. The histopathology of the specimen resected (figure 2) showed extensive intramural haemorrhage involving submucosa and extending through muscularis into serosa. There was no histological evidence of LCH involvement and the CD 1a antigen was negative. There was no evidence of a vasculopathy. There were multiple areas of superficial mucosal ulceration.

### Figure 2

Histopathology of resected specimen showing extensive intramural haemorrhage/haematoma(a); Jejunal serosa(b); Superficial jejunal erosions(c).



Five days post surgery, there were further intermittent decreases of haemoglobin, and melena were noted and continued for two weeks. Further management included naso-gastric decompresson of her stomach, total parenteral nutrition, transfusion of blood products as required and a short course of recombinant human coagulation Factor VIIa and tranexamic acid to help manage significant ongoing bleeding. The post operative period was further complicated by a protein losing enteropathy and

hypogammaglobulinemia that was managed with weekly immunoglobulins.

Vinblastine was resumed one week post surgery and intravenous hydrocortisone replaced oral prednisolone two weeks, and she was not given food by mouth. Our patient was successfully discharged home about 6 weeks after the onset of bleeding. Unfortunately at 3 months follow up she has shown signs of LCH progression and treatment intensification has begun with further courses of vinblastine, prednisolone and addition of methotrexate.

## DISCUSSION

LCH involvement of the gastrointestinal tract is rare (2.6% incidence) and carries a poor prognosis. Its peak incidence is in children from 1 to 4 years [9]. It frequently present with haematochezia and a protein losing enteropathy [9,10]. Although our patient was subsequently diagnosed with a protein losing enteropathy, histological and immunological analysis of her resected duodenum and proximal jejunum were negative for LCH involvement. Hence the duodenal intramural bleeding noted in this patient was unlikely to have been related to her LCH. Moreover, there have been no reports of duodenal intramural haemorrhage in LCH. The duodenum is prone to intramural haemorrhage because

of its generous blood supply and its rich submucosal vascular plexus. Its serosal layer is not circumferential so the bowel wall varies in elasticity. Furthermore, it is bound by the pylorus, aortic-superior mesenteric vascular angle and ligament of Treitz. This results in a 'physiologic closed loop' rendering it susceptible to sudden increases in intraluminal pressure seen in abdominal trauma. Trauma and coughing can cause stretching and relaxation of the bowel wall capable of tearing submucosal vessels. The absent serosal layer in the retroperitoneal portion limits its ability to tamponade active intramural haemorrhage [11-13]. Blunt abdominal trauma is the most common cause of duodenal intramural haemorrhage in children. However, the injury is sometimes trivial or unrecognized. The relatively fixed retroperitoneal position of the duodenum, its adjacent anterior relationship to the lumbar spine, and the less developed abdominal musculature in children increases their predisposition to crushing trauma [12,13]. Janic and coworkers [14] postulated that coughing due to pneumonia may have predisposed their patient with severe haemophilia A to intestinal intramural haematoma. Jones and co-workers [12] reported the development of an intestinal intramural haematoma case due to severe hiccoughs. The patient discussed in this report did have significant coughing episodes preceding her intramural haemorrhage. Hence, coughing could have been responsible for the child's duodenal intramural bleeding.

Duodenal intramural bleeding is strongly associated with blood dyscrasias like Hemophilia, von Willebrand's disease, and idiopathic thrombocytopenic purpura [7,8,12,15]. There was no evidence of a coagulopathy in the girl in this case report. Vinblastine can precipitate bleeding due to thrombocytopenia [16]. Haemorrhagic enterocolitis is a potential adverse effect of vinblastine. However, our patient had normal platelet counts and coagulation screens at the onset her of her bleeding. Therefore, the duodenal bleeding, was most likely not due to vinblastine. Systemic steroids can almost double the risk of upper gastro-intestinal bleeding or perforation in the adult population [17]. However, there have been no previous reports of intestinal intramural haemorrhage attributed to steroid use.

Bleeding and vascular defects have been reported in the Ivemark syndrome and in situs inversus, conditions related to heterotaxy [18, 19]. However, intramural intestinal haemorrhage has not been reported in these conditions and there was no evidence of a vasculopathy in the resected specimen.

In Conclusion, the aetiology of intramural haemorrhage in

this case remains unexplained. Trauma due to coughing is a possible cause. Local duodenal LCH involvement, chemotherapy and heterotaxy were considered but were thought to be unlikely causes.

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