CASE REPORT

Sudden death of a patient with primary hypereosinophilia, colon tumours, and pulmonary emboli

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A 33 year old man was admitted to hospital six days after the onset of abdominal pain. There was hypereosinophilia, but the cause could not be identified (primary hypereosinophilia). The hypereosinophilia, high C reactive protein concentration, and gastrointestinal symptoms were alleviated by corticosteroid treatment. Unexpectedly, after this apparent recovery, he was found dead on the 27th day after admission. Necropsy disclosed two solid tumours primarily composed of eosinophils in the ascending and transverse colon. The cause of the sudden death was pulmonary artery emboli, derived from a thrombus in the left iliac vein.

Hypereosinophilia (HE) is caused either by parasite infection, allergic diseases, drugs (secondary HE), or unknown causes (primary HE).¹ The lung, skin, intestine, and peripheral nerves are affected by allergic vasculitis and granulation in some patients with HE. Most of these patients respond to corticosteroid or immunosuppressive treatment. However, patients with HE sometimes die suddenly of myocarditis, eosinophilic endomyocardial fibrosis (Loeffler's endomyocarditis), myocardial dysfunction (congestive heart failure), or thrombotic hypertrophic mitral-tricuspid valve disease. It was previously reported that hypercoagulation as a result of HE causes biventricular apical and pulmonary artery thrombi,² portal vein thrombosis,³ and disseminated intravascular coagulation.⁴

This is the first report on a sudden death caused by pulmonary emboli derived from deep vein thrombosis in a patient with primary HE who also had solid intestinal tumours.

CASE REPORT

A 33 year old man was admitted to hospital six days after the onset of abdominal pain. He had leucocytosis with hypereosinophilia (with a peak ratio of 43.5%; fig 1), a high C reactive protein concentration, and symptoms of pancreatitis, enteritis, and peptic ulcer, but no symptoms of allergic or parasitic diseases. An abdominal computerised tomography scan revealed slight thickness of the gastric wall, but no tumour. Gastroendoscopy also showed mild duodenum ulcer. These symptoms and findings were alleviated by corticosteroid treatment. Laboratory examinations did not identify common causes of HE, such as parasitic and allergic diseases, whereas the gastrointestinal biopsies showed severe mucosal infiltration of eosinophils, which had disappeared by the time the necropsy was performed. The bone marrow aspiration showed high ratios of eosinophils to leucocytes (mature, 29.8 immature, 9.8) and myeloid to erythroid cells (10.8). The total cell numbers of myeloblasts (0.2%), lymphocytes (14.4%), and monocytes (2.2%) were all within the normal ranges. Skin biopsy showed proliferative thromboangitis with eosinophilia. These data led us to diagnose primary HE, but

not leukaemia. The eosinophil count, IgE value, and symptom severity were normalised by corticosteroid treatment (fig 1). On the 27th day, he was found unconscious in the toilet. Despite resuscitation for four hours, he finally died.

At necropsy, two solid and rigid tumours were found at the end of the ascending colon (4 × 3.5 × 2 cm) and the transverse colon (3.3 × 2.5 × 1.5 cm) (fig 2A). These tumours were encapsulated, demarcated in the serosal surface, and protruded into the intestinal cavity (fig 2B, C). There was neither eosinophilic infiltration nor inflammation in the other portions of the colon and small intestine on histological examination. Haematoxylin and eosin staining showed infiltration of binuclear eosinophilic cells, with few granules within the tumours (fig 2D). Immunostaining for an eosinophil marker (anti-major basic protein; 1/20 dilution; Monosan AM, Uden, The Netherlands) showed that the tumour was composed primarily of eosinophils (fig 2E, F), although there was mild fibrosis. There was no staining for leucocytes (antimyeloperoxidase), epithelium (antikeratin; 1/700 dilution; Dako, Glostrup, Denmark), epithelial membrane antigen (1/100 dilution; Dako), lymphocytes (anti-CD45; 1/50 dilution; Dako), or plasma cells (anti-κ chain; 1/200 dilution; anti-λ chain; 1/200 dilution; Novocastra, Newcastle, UK).

There were multiple thrombi in the major trunks of the right and left pulmonary arteries (fig 3A), and a large thrombus in the proximal portion of the left iliac vein, with whitish fibrous caps adhered to the vascular wall (fig 3B). Histology (Elastica-Masson staining) showed laminar lines of fibrin in the pulmonary artery thrombi (fig 3C), indicating the age of the thrombi (more than a few days).

There was no pancreatitis or peptic ulcer in the gastrointestinal tract and no injury (including legs) in the postmortem findings.

DISCUSSION

This is the first report of an eosinophil derived solid tumour in any organ, including the intestine. The tumour was distinct from eosinophilic enteritis. During hospitalisation, the gastric and intestinal infiltration of eosinophils was confirmed by biopsy. However, at necropsy neither eosinophilic infiltration nor inflammation was evident in the colon and small intestine, probably because of the steroid treatment. The cells in the tumours had few eosinophilic granules, suggesting their immaturity. The immature eosinophils were also seen in the bone marrow during hospitalisation. Although sudden death as a result of eosinophilic myocarditis has been reported,⁵ we found no eosinophilic infiltration. It is likely that the two tumours protruding into the intestinal cavity would have caused the obstructive intestinal ileus and the abdominal pain.

Abbreviations: HE, hypereosinophilia

Figure 1 Temporal changes in the number of white blood cells (WBC), ratio of eosinophils to the leucocytes, and serum IgE values.

The patient died of pulmonary artery emboli, derived from deep iliac vein thrombosis. It has been suggested that eosinophils cause hypercoagulation, probably through invasive tissue damage and tissue factor exposure,⁶ as malignant tumours do. Consistent with this hypothesis, the four major proteins secreted from eosinophils—major basic protein, eosinophil derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase—are potent and non-specific cytotoxins.⁷ In addition, these four granule proteins may promote platelet activation and coagulation. For example, major basic protein and eosinophil peroxidase can release 5-hydroxytryptamine, a potent platelet activator.⁸ Eosinophil cationic protein accelerates coagulation through a factor XII dependent mechanism.⁹ Moreover, the four eosinophil derived proteins inhibit the anticoagulation activity of thrombomodulin on the endothelial and endocardial surface.¹⁰

“It has been suggested that eosinophils cause hypercoagulation, probably through invasive tissue damage and tissue factor exposure”

Thrombosis can be caused by either of three factors: blood stasis, injury to a vein, or hypercoagulability. First, the patient was allowed to move relatively freely, in contrast to the absolute bed rest usual in patients with leg fracture,

Figure 2 (A) The two tumours at the end of the ascending and transverse colon are indicated by the arrows. (B) In the transverse section of the transverse colon, the whitish demarcated tumour protruded from the serosa on the left, whereas the intestinal lumen and wall appeared intact in the upper right portion. (C) Low (original magnification, $\times 40$) and (D) high (original magnification, $\times 600$) power fields of the tumour (haematoxylin and eosin staining). In (C) the tumour and normal intestine are seen to the left and right, respectively. In (D) it can be seen that the tumour was composed mostly of eosinophils. The tumour cells are stained positively for (E) major basic protein (original magnification, $\times 40$, left hand side) in (F) the cytosol (original magnification, $\times 600$).

Figure 3 (A, B) Thrombi in the major trunks of the pulmonary artery (arrows) and a large thrombus in the proximity of the left iliac vein. (C) Laminar lines of fibrin in the pulmonary artery thrombosis (Elastica-Masson staining; original magnification, $\times 20$).

Take home messages

- This is the first report of primary hypereosinophilic syndrome with solid colon tumours and sudden death caused by pulmonary emboli
- It remains to be elucidated how hypereosinophilia leads to the development of a tumour
- We speculate that in this patient intrinsic hypercoagulation resulting from hypereosinophilia contributed to the extensive left iliac vein thrombosis under relatively light bed rest

major surgery, brain injury, or haemorrhage. The colon tumour could not have compressed the iliac vein. However, it is known that occasionally thrombosis can be caused in the left iliac vein by iliac artery compression, as in our case. There was neither deep vein injury in the lower extremities nor medical practices that can cause vessel injury. Accordingly, it is tempting to speculate that the intrinsic hypercoagulation state as a result of hypereosinophilia contributed to the extensive left iliac vein thrombosis under the relatively light bed rest.

In conclusion, we present the first case of the primary hypereosinophilic syndrome with colon solid tumours and sudden death caused by pulmonary emboli. It remains to be elucidated how hypereosinophilia leads to the development of a tumour.

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