CASE REPORT

Rare cause of fever of unknown origin: gastrointestinal stromal tumour

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SUMMARY

A 44-year-old man presented with fever (low to high grade) for 2-month duration despite treatment with oral antibiotics and antipyretics. Further, enquiry did not yield any potentially explanatory clues to a diagnosis. Physical examination revealed only left axillary lymphadenopathy, but was otherwise unremarkable. A number of diagnosis included tuberculosis, malignancy, lymphoma, connective tissue disorder and infective endocarditis. Further evaluation revealed severe anaemia due to iron deficiency which was supported with blood transfusion and oral iron supplementation. Septic work-up including blood cultures and urine culture sterile and procalcitonin, but all these proved negative. Transthoracic echocardiography followed by transoesophageal echocardiography did not reveal any vegetations suggestive of infective endocarditis. Contrast-enhanced CT of chest and abdomen showed a polypoidal mass in the caecum. Lymph node biopsy from left axillary lymph node showed changes consistent with reactive hyperplasia. A bone marrow biopsy was inconclusive. Mantoux test was negative. A colonoscopy revealed a polypoidal growth arising from caecum with dull-looking mucosa. Biopsy of the mass suggested a leiomyoma. Positron emission tomography CT showed fluorodeoxyglucose (FDG)-avid caecal mass with FDG-avid mesenteric lymph nodes (figure 1). In spite of extensive work-up, we could not find a source of the fever except for caecal mass. Thus, in the absence of other explanatory findings, a decision for resection of the mass was taken. A laparoscopic right hemicolectomy done with primary anastomosis. Histology confirmed a gastrointestinal stromal tumour (figure 2, which was smooth muscle actin positive (figure 3), S-100 positive, vimentin positive, but c-KIT negative (figure 4), CD34 positive and desmin negative. Additional immunohistochemistry and gene mutational analysis could not be done due to resource limitations. The postoperative course was good, and the patient was followed for 9 months after surgery with good clinical recovery and no further fever. This case illustrates the need for high index of suspicion to diagnose malignancy as cause of fever.

BACKGROUND

Fever of unknown (FOU) origin can be manifestation of occult malignancy. However, the evaluation and search for the cause of fever in case of

FOU is one of the most challenging task for the physician as highlighted by this presented case of gastrointestinal stromal tumour (GIST).

CASE PRESENTATION

A 44-year-old male resident of a rural area in India, with no other comorbidity presented with fever (high grade, associated with chills and rigors) for 2 months, associated with loss of appetite and loss of some weight. Further, detailed and repeated history taking did not elicit any localising symptoms. No history of blood transfusion, no history of intravenous drug abuse, no history of unprotected sexual activity, no history of recent travel, no history of skin rashes and joint pain. Meticulous general physical examination revealed left axillary lymphadenopathy (non-tender, firm in consistency) and severe pallor. At the time of presentation, the patient was alert and febrile, with tachycardia (pulse rate of 120 beats per min, blood pressure of 130/80 mm Hg) and respiratory rate of 18/min. The remainder of systematic examination was absolutely normal.

INVESTIGATIONS

Haematological and biochemical investigations revealed severe anaemia with microcytic hypochromic anaemia (Hb 6.9 g/dL) with thrombocytosis (555 000/ μ L) and leucocytosis (17 700 per μ L). Patient had systemic inflammatory response (SIRS=3/4, raised leucocytes, tachycardia and raised body temperature, ie, temperature >100.4°F). Iron profile was consistent with iron deficiency (serum iron 30 μ g/dL, total iron-binding capacity 394 μ g/dL and percentage saturation 8%) but stool for occult blood was negative. IgA TTG (Tissue transglutaminase) done suspecting coeliac disease was also negative. Iron deficiency anaemia was attributed to nutritional deficiency considering the fact that patient is from rural background and he is strict vegetarian along with decreased appetite for the duration of disease. Coagulogram study was normal. Liver function tests were normal except for isolated elevation of alkaline phosphatase (ALP)=449 IU/L. We attributed raised ALP to intestinal origin in the view of damaged intestinal mucosa secondary to the polypoidal mass with normal levels of bilirubin, gamma glutamyl transpeptidase, vitamin D, calcium, phosphorus and intact parathyroid hormone and no intrahepatic biliary radicle dilatation on ultrasound. Erythrocyte

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Figure 1 Fluorodeoxyglucose (FDG)-avid caecal mass with few mesenteric lymph nodes showing FDG avidity.

sedimentation rate was markedly elevated to 131mm and even C reactive protein was elevated to 958mg/dL. Antinuclear antibody done for autoimmunity disorder was negative. Septic work-up including blood and urine cultures was negative. Procalcitonin was normal (0.25 ng/mL). Malaria, dengue fever and scrub typhus (IgM) serology were negative. Widal test was negative. Transthoracic followed by trans oesophageal echocardiography did not show any vegetations/clots suggestive of infective endocarditis. Viral markers such as HIV, hepatitis B virus surface antigen (HBsAg) and antihepatitis C virus were non-reactive. Lymph node biopsy from left axillary lymph node was suggestive of reactive lymph node hyperplasia. Even after extensive work-up, we could not attribute left axillary lymphadenopathy to any definitive cause and it remained idiopathic. Mantoux test was negative and chest X-ray was clear. An ultrasonography of abdomen showed splenomegaly. Contrast-enhanced and high-resolution CT chest and abdomen showed an endoluminal, heterogeneous, polypoidal lesion arising from the caecal wall measuring approximately 5.6×4.5×4.7cm with few enlarged lymph nodes in ileocolic mesentery. Bone marrow examination done in the view of FOU origin but it was inconclusive. Cytomegalovirus RNA was negative. Colonoscopy done for suspected caecal lesion revealed polypoidal growth arising from caecal wall with dull-looking mucosa. Biopsy was taken from the lesion and it came out to be leiomyoma. Fluorodeoxyglucose (FDG) positron emission tomography was done, which showed

Figure 2 Histopathology showing spindle-shaped cells arranged in whorl pattern suggestive of gastrointestinal stromal tumour.

Figure 3 Immunohistochemistry showed Anti smooth muscle actin antibody positive.

FDG-avid caecal mass with FDG-avid mesenteric lymph nodes (figure 1). Postsurgery histology report was suggestive of gastrointestinal tumour. The individual tumour cells showed moderate pleomorphism, round to spindle-shaped vesicular nucleus and moderate amount of clear to eosinophilic cytoplasm (figure 2). Area of haemorrhage and intervening chronic inflammation noted. Small foci of necrosis noted. On performing immunohistochemistry, these tumour cells showed strong diffuse positivity for anti-smooth muscle actin antibody (figure 3) and vimentin, focal positivity for S-100, whereas negative for C-KIT (figure 4), CD34 and desmin.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis considered were tuberculosis, HIV, connective tissue disorder and malignancy. But extensive work-up for infective causes and autoimmune disorders were negative. Finally, biopsy from caecal mass clinched the diagnosis of GIST.

TREATMENT

Patient was initially started on antipyretics along with empirical antibiotic cefoperazone and sulbactam. Severe iron deficiency with anaemia was supported with 2-unit blood transfusion and

Figure 4 Tumour was negative for c-KIT.

oral iron therapy. But after exclusion of infective aetiologies as mentioned above, intravenous antibiotic was stopped and only antipyretic on *si opus sit* basis continued. Due to persistent fever, he was planned to undergo laparoscopic-guided right hemicolectomy with anastomosis for GIST in caecum.

OUTCOME AND FOLLOW-UP

The patient was followed for 9 months after surgery and he is completely afebrile and doing well. He started gaining weight, with no abdominal pain, bleeding per rectum and obstructive symptoms like constipation/obstipation. Imatinib was not started as the tumour was localised and low grade.

DISCUSSION

Differential diagnoses for a middle-aged adult presenting with fever for long duration with no localising symptoms include deep-seated bacterial infections like infective endocarditis, disseminated tuberculosis, connective tissue disorders, drug fever and malignancy. It is noteworthy to know that even though malignancy is rare cause of fever, having high suspicion for malignancy helps to detect it at earlier stage and may enhance the further prognosis after treatment.

GISTs represent the most common mesenchymal tumour of gastrointestinal tract (GIT).¹ Even though some series show male predilection, there is usually no sex predilection.¹ GISTs can be distinguished by the presence of mutations in c-KIT proto-oncogene.² In our case GIST was negative for c-KIT. There are recent reports of c-KIT negative GISTs. GISTs can occur anywhere along the GIT with stomach and small intestine being the most common locations.² GIST also occurs as a part of carney triad (GIST, paraganglioma and pulmonary chordoma) in young women. Most of the patients present with vague symptoms such as nausea, vomiting, abdominal discomfort, weight loss or early satiety with site-specific symptoms like dysphagia, haematemesis, melena, jaundice and intestinal obstruction. Lymph node metastases are uncommon in GISTs. To our knowledge there is no case report of GIST presenting solely as fever.

The aetiology of fever has not been definitively explained in case of GIST. We think cause of fever in GIST can be both infective or non-infective inflammatory causes. Damaged and unhealthy mucosa may be a fertile soil for infection. Necrosis of tissue with phagocytosis of damaged tissue might initiate release of cytokines and interleukins (ILs) like tumour necrosis factor alpha and IL-1 and thus increasing body temperature. To support this hypothesis, our patient had systemic inflammatory response. However, exact mechanism of fever in GIST remains speculative.

Microscopically three main histological subtypes have been accepted, most common variety being spindle cell type (70%), epithelioid type (20%–30%) and mixed spindle cell and epithelioid type.

The only potentially curative treatment of GISTs still is complete surgical resection of the tumour burden if it is a locally resectable or marginally resectable tumour. Lymph node

Patient's perspective

As narrated by patient himself (translated from Hindi to English), My disease was detected at earliest time possible. And I was advised for surgery as last solution to my problem. Due to God's blessing surgery went good and no complications occurred. After surgery I am really feeling good and no fever since 8 months after surgery. I have been having good appetite and regain of weight (as told during subsequent visits).

Learning points

- ▶ Treating physicians should always have strong suspicion for underlying undiagnosed malignancy as cause of fever while evaluating the aetiology of fever of unknown origin.
- ▶ Sometimes fever can be the only manifestation of occult malignancy thereby leading to early detection of tumour.
- ▶ Early detection and removal of gastrointestinal stromal tumour will be curative.
- ▶ Though erythrocyte sedimentation rate (ESR) is very non-specific, extreme elevation of ESR >100, must alert physician to think for inflammatory/neoplastic causes apart from common infective aetiologies.

resection is not required as it rarely metastasise to lymph nodes. The Food and Drug Administration has approved imatinib as adjuvant therapy. Most guidelines recommend adjuvant imatinib for at least 1 year following complete surgical resection in patients with intermediate-risk to high-risk GIST. Treatment with imatinib now is the standard care for patients with locally advanced, recurrent or metastatic disease.³

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