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Severe Eosinophilia in Disseminated Gastric Carcinoma

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ABSTRACT

Peripheral blood eosinophilia is a well-recognised but unusual manifestation of malignancy, and may represent a paraneoplastic phenomenon. We present a case of poorly differentiated adenocarcinoma of the stomach associated with severe peripheral blood eosinophlila A 55-year old man was admitted for abdominal pain of one week duration. An incidental finding of leucocytosis with eosinophilia was noted. After excluding haematological and infectious causes, an oesophagogastroduodenoscopy (OGD) followed by biopsy confirmed the diagnosis. Eosinophilia appears to be a response to cytokine production, and treatment is aimed at the underlying malignancy, and reducing the eosinophil count when necessary, to prevent end-organ damage. Studies have shown that peripheral eosinophilia is associated with disseminated, metastatic disease and hence signifies a poor prognosis, whereas tissue eosinophilia in advanced cancer has a better survival rate.

Keywords: Peripheral eosinophilia, gastrc carcinoma, metastatic disease, poor prognosis

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CASE REPORT

A 55-year-old Malay man with a history of non-insulin dependent diabetes mellitus (NIDDM), chronic pancreatitis, treated tuberculosis and lung aspergilloma, presented with colicky abdominal pain of one week's duration. This was associated with loss of weight and appetite with early satiety of one month's duration. On examination, he was cachectic and febrile (38.1°C). There was generalised tenderness in the abdomen with guarding and rebound tenderness. Abdominal masses were not palpable. Bowel sounds were absent.

Chest X-ray films showed consolidation with partial atelectasis and cavitation in the upper lobe of the right lung, similar to films taken previously. The haemoglobin leve1 was 1l.4 g/dL, leucocyte level was markedly raised at 49.34 x 10^9/L (70.1% polymorphs, 19.9% eosinophils), and the platelet count 359 x 10^9/L. Clinical features and preliminary investigations suggest an infective process, possibly a liver abscess. Antibiotic therapy with intravenous ceftriaxone and metronidazole was begun empirically. Abdominal X-ray showed calcifications consistent with chronic pancreatitis. Computed tomography (CT) of the abdomen revealed multiple hypodense lesions in the spleen and the liver. There was no significant para-aortic lymphadenopathy. This was consistent with the diagnosis of multiple abscesses or metastatic lesions. These lesions were not seen in a similar CT abdomen done 6 months earlier. CT thorax showed scarring in both upper lobes as well as a thick wall cavity with irregular soft tissue mass consistent with tuberculosis with mycetoma formation. No adrenal masses or thoracic spine lesions were seen. Blood culture grew coagulase negative Staphylococci, but no fungal growth. Sputum had moderate growth of Candida albicans but was negative for acid-fast bacilli. Serology for Aspergillus, amoeba, meliodosis as well as HIV were negative. Immunoglobulin levels were fairly normal with the exception of IgE which was markedly raised at 3939.0 U/mL (10 ~ 180). CD4 and CD8 levels were normal with a ratio within normal range. In view of the investigative findings, he was treated as for infection. The possibility of a fungal or parasitic infection could not be excluded. Eosinophilia was thus attributed to a fungal infection, possibly a recurrence of aspergilloma. He responded well to antibiotics and the fever subsided after 3 days. Symptoms improved and he remained clinically well.

Two weeks later, a repeat CT abdomen was done. The appearance of the lesions were unchanged, and probably represented metastatic lesions. Tumour marker levels, alpha-foeto protein (αFP) and Carcinoembryonic antigen (CEA) levels were within normal range, but CA 19-9 was markedly raised at 1618.0 U/mL. Meanwhile, blood counts showed a steadily increasing leucocyte level from 41.0 ~ 88.11 x 10^9/L and an increasing eosinophil count from 23.0 ~ 38.3%. An oesophagogastroduodenoscopy (OGD) was performed in July 1998. It revealed a 2 cm diameter ulcerated lesion in the cardia. Histology showed a poorly

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differentiated adenocarcinoma of the stomach.

A bone marrow aspirate and trephine showed normocellular marrow (cellularity of 60%) with adequate number of megakaryocytes and a predominance of the myeloid series. There was no metastatic disease seen. Bone marrow cytogenetic analysis was normal, having cells with 46 XY karyotype. Bone scan had no evidence of metastasis. However, in view of the extensive metastatic disease to the liver and spleen, as well as the limited benefits of chemotherapy, in addition to consideration for his age and health condition, it was decided that palliative and supportive management be the mode of treatment for him. Leucocyte count however continued to climb to 127.7 x 10^9/L with an eosinophil count of up to 56%. Hydroxyurea 500mg om was begun. He was discharged five weeks later, and has since defaulted follow up.

DISCUSSION

Eosinophilia is the abnormal accumulation of eosinophilic polymorphonuclear leucocytes in the blood or tissues, and normally accounts for only 1 to 3% of peripheral blood leucocytes, but has a normal range of up to 6%[1]. The most common cause of eosinophilia world-wide is helminthic infections, while the most common cause in industrialised nations is atopic disease[2]. Malignancy is a well recognised but unusual cause of peripheral eosinophilia, and may occur as a component of the disease or as part of a paraneoplastic syndrome. Other less common causes include collagen vascular diseases, drugs and eosinopohilic syndromes where accumulation is limited to specific organs. The idiopathic hypereosinophilic syndrome is a diagnosis of exclusion and should be considered in the absence of an identifiable cause of moderate to severe eosinophilia and in the presence of end-organ damage.

About 1% of eosinophilia is associated with malignancies[3] but moderate eosinophilia is seen in 5 to 15% of malignant tumours[4]. The first case of malignant tumour associated with marked blood eosinophilia was described by Reinback[5] who in 1893, reported a case of carcinoma of the neck associated with eosinophilia. Total white blood cell count was 120 x l0^9/L with 48.84% eosinophils. Since then, eosinophilia has been observed and described in many cases of carcinoma from various organs including the breast[1], lung[6], cervix[7], liver[8], pancreas[9,18], thyroid[11,12] and the stomach[4,13] amongst many others.

The pathogenesis of eosinophilia in malignancy is not clear, but appears to occur as result of four disease processes[2]: (1) The tumour and/or its cell lines cause differentiation and proliferation of eosinophils in response to cytokines[8], which may be overproduced in malignant conditions. Cytokines have also been shown to prolong their lifespan[2,23]. (2) Migration into the blood and tissues occur and is directed to a specific location by (3) chemoattraction. This is followed by, (4) their activation and destruction.

The significance of eosinophilia in gastric cancer lies in the fact that studies have shown a close association between the prognosis of gastric cancer and the presence of local or systemic eosinophilia. Iwasaki et al[12] demonstrated that invasive poorly differentiated tumours tend to have a higher degree of blood eosinophilia. Generally, peripheral eosinophilia that is associated with tumours represents a late manifestation, as has been demonstrated in our case report, and may thus be a potential marker of widespread disseminated disease[7,9,10,15]. This is correlated with a poorer prognosis of the tumour[15]. Similarly, it may also be used by clinicians as a marker for tumour persistence after radiotherapy[13,16] or for indication of a relapse[10,13]. In contrast, for patients with such advanced cancer, survival rates were significantly better in those with moderate to marked tissue eosinophilic infiltration than those with few or no eosinophilic infiltration[7].

In most patients, eosinophilia is asymptomatic, and, like our patient remains completely well. Symptoms are more likely to be a manifestation of the primary tumour itself. In most instances, eosinophilia is only identified incidentally on a complete blood count (CBC), as it was in our patient. However, it has been suggested that once a critical level of eosinophilia is exceeded, tissue and organ damage ensues regardless of the underlying cause[17,18]. For example, in severe eosinophilia, infiltration of tissues especially that of lung may occur, resulting in shortness of breath and wheeze. Chest X-rays may then show diffuse pulmonary infiltrates.

Eosinophilia rarely contributes to an increase in mortality except in unusual cases such as that associated with endomyocardial fibrosis[13]. It is treated with drugs which aim to reduce eosinophilia counts or block the detrimental effects of eosinophil products to prevent end-organ damage. These agents include glucocorticoid[19], myelosuppressive drugs (e.g. hydroxyurea, vincristine) and interferon-alpha[20]. Second line drugs such as leukotriene antagonist[21] and third-generation anti-histamines[22,23] (e.g. cetirizne) have also been described by various authors. However, the definitive management is aimed at treating the underlying malignancy. Symptomatic relief may be achieved with glucocorticoids. Hydroxyurea, an antimetabolite, was used in our patient as a palliative treatment to decrease leucocyte and eosinophil levels to prevent any possible end-organ damage.

In conclusion, eosinophilia associated with malignancy is more than an interesting side phenomenon – it may represent an important disease marker of

extensive metastatic disease with prognostic significance[7,9,13,18]. It may even rarely cause disease on its own.

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