Case Report

Two nights in one day: A case report of paraganglioma in sickle cell disease and a review of the literature

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Abstract

Background: Sickle cell disease (SCD) is a chronic lifelong disease seen typically in Sub-Saharan Africans, the Mediterranean region and parts of Asia. The condition may be associated with other clinical entities.

Aim of Presentation: We present a case of malignant variant of paraganglioma in a 34-year-old SCD patient to highlight the fact that some very rare clinical entities may be found in this category of patients.

Case Report: Miss B.O. was a 34-year-old SCD patient who presented with features of an intra-abdominal mass. Incisional biopsy done from a mass arising from the left adrenal gland confirmed a malignant variant of paraganglioma. Post-exploratory laparotomy, the patient's clinical state deteriorated and she died 25 days after surgery.

Conclusion: Malignant variant of a paraganglioma, a very rare clinical condition, may be found in SCD patients.

Keywords: Malignant paraganglioma, rare condition, sickle cell disease

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INTRODUCTION

Sickle cell disease (SCD) is a chronic lifelong disease seen mostly in Sub-Saharan Africans, the Mediterranean region and parts of Asia. It is due to a mutation in the gene coding for the beta chain of haemoglobin (Hb).[1,2] Affected people have the abnormal HbS, which causes the red blood cells to be malformed and sickle shaped.[1,2] It is among the most common genetic disorders seen in Africa, the United Kingdom and in many other countries.[1,2] Several reports indicate an increase in the risk of malignancy in SCD. This increased risk involves both the more common haematological cancers as well as solid tumours.[3-12]

There is, however, a dearth of data on the range of cancers involved. Solid tumours are rare and include colon cancer (relative risk [RR] 2.8, 1.2–5.5), non-melanoma skin cancer (RR 4.4, 1.3–12.2), kidney cancer (RR 5.4, 2.3–11.5) and thyroid cancer (RR 5.1, 1.3–15.4).[13]

Paragangliomas are an extremely rare type of solid tumours derived from cells of the extra-adrenal paraganglia which are rudiments of the autonomic nervous system. They have an incidence of 2–8 cases per million persons per year and a prevalence of 1:6500–1:2500.[14] Although mostly benign, 10%–15% will undergo malignant change.[15-17] Phaeochromocytomas are the most common subtype.[18]

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They are highly heritable when compared to most other cancers with 40% showing germline mutations in one or more of up to thirty possibly causative genes.[19,20] Up to a quarter of these develop under conditions of the hereditary tumour syndrome, mostly the Von Hippel–Lindau gene.[21]

Paraganglioma in an SCD patient, therefore, represents the coexistence of two distinct pathologies of with strong genetic basis.

This case report intends to draw attention to the possibility of a genetic link between the two and to provoke further research into the possibility that there are linked genetic or epigenetic mechanisms as explanation for this finding.

CASE REPORT

A 34-year-old female applicant, known SCD (HbSS) patient for more than 22 years presented to our facility on 11 February 2018 with a 1-year history of generalised abdominal swelling. The swelling was of insidious onset, progressive but has been much more rapid over the last 2 months.

There is associated moderate, dull-aching, constant and generalised pain. There was also occasional constipation, anorexia and weight loss. These symptoms were very similar to the features of SCD, and she has had for almost two decades.

She has about three to four sickle cell crises yearly, latest crisis was 7 weeks before and treatment usually included rehydration, blood transfusion, antibiotics, analgesics and antimalarials. She is not aware of family history of cancer, no prior irradiations and has never been on hydroxyurea.

On examination, she was chronically ill-looking, warm to touch, dehydrated, pale, icteric with sickle cell habitus.

Abdomen was distended, had generalised scarifications, moved with respiration and was soft.

There was a mass in the left half of the abdomen and entire pelvis and measured 25 cm by 14 cm. It was firm, tender, nodular and fixed. There was guarding, rebound tenderness, ascites but no hepatosplenomegaly. Bowel sounds were absent.

Rectal examination revealed a bulging, firm and tender anterior rectal wall. Examining finger was stained with melaena.

Her pulse was 106/min, blood pressure was 100/60 mmHg and heart sounds 1 and 11 were present.

Respiratory rate was 28/min, SPO_2 was 98% and admitting packed cell volume was 22%.

Other systems were essentially normal.

An impression of peritonitis following bleeding intra-abdominal tumour was made.

She was resuscitated with intravenous fluids, transfused four units of blood, antibiotics and analgesics.

A nasogastric tube and urethral catheter were passed and blood samples were collected for complete blood count, serum electrolytes, urea and creatinine. Informed consent was obtained for laparotomy. At surgery, findings were 800 ml of bloody ascitic fluid, huge intra-abdominal mass occupying pelvis and left half of the abdomen up to hypochondrium displacing gut to the right upper abdomen. Mass is retroperitoneal, fixed and nodular, and there were many mesenteric and omental lymph nodes.

Ascitic fluid was collected for microscopy, culture and sensitivity, and peritoneum was suctioned dry. Biopsy was taken from the mass and abdomen closed in layers.

Post-operatively, we continued intravenous fluids, antibiotics, blood transfusion, analgesics and a dose of tranexamic acid, 500 mg. The abdominal wound did well, but her clinical state was poor and her performance status as assessed by the Eastern Co-operative Oncology Group system remained poor. She had features of sepsis, anaemia and progressive organ failure until her demise 9 weeks after presentation.

Figures 1 a-c (H and E) show the photomicrograph of the slides showing the nest or insular pattern of paraganglioma.

Figures 1d-g (immunohistochemistry) show clusters of delicate fibrovascular stroma separating relatively uniform polygonal cells into nest and clusters giving it the Zellballen pattern. These cells are surrounded by sustentacular cells.

DISCUSSION

SCD is caused by a mutation in the gene coding for the beta chain of Hb located in the short arm of chromosome 11. It was first scientifically described in 1910 by James Herrick and is now the most common genetic disorder in many countries.[22,23]

Similarly, paraganglioma is a strongly heritable disease when compared to other cancers.[19,20]

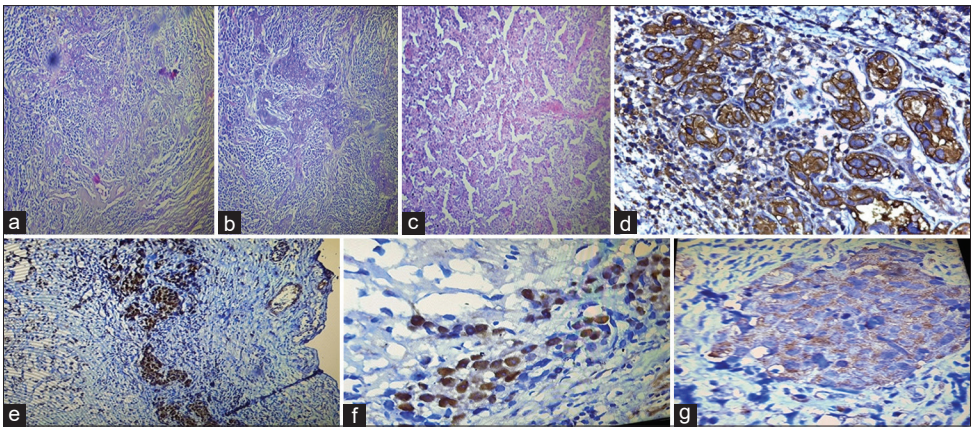

Figure 1:

The coexistence of paraganglioma and SCD, two distinct pathologies with very strong genetic basis immediately throws up many possibilities. This is more plausible when weighed against the backdrop of ongoing research on associations between different diseases especially on how carriers of certain abnormal genes may have increased or reduced risk of suffering certain cancers.[24-26]

Suggested aetiopathogenetic mechanisms for this altered cancer risk in SCD include malignant transformation of tissues chronically damaged by the cytopathological consequences of SCD such as chronic inflammation,[9] the finding of elevated proangiogenic markers associated with vascular complications of SCD[27] and transmission of carcinogenic viruses via blood transfusion in SCD.[28]

Hydroxyurea, widely used in the management of SCD, has also been widely reported as a possible cause of increased cancer risk in such patients. It inhibits DNA synthesis and repair and *in vitro* suppresses complete DNA repair, thus promoting the accumulation of mutations and chromosomal damage.[29-31] These effects were well-recognised mechanisms in carcinogenesis. It is also very probable that the severe and prolonged immunosuppression pre- and post-bone marrow transplantation therapy in SCD predisposes to cancer.[32-34]

It is possible, therefore, that SCD alters a person's cancer risk by both genetic and epigenetic interactions that eventually lead to the development of cancer, especially those cancers with a very strong genetic basis. This possibility and the underlying aetiopathogenetic mechanisms will become clearer with advancements in research more so as the life expectancy of SCD patients continues to improve. In a review by Thomas *et al*., of the 85 deaths amongst SCD patients, 11 cases were from various types of malignancies.[35] One of the cases was that of extra-adrenal metastatic paraganglioma. Similarly, Seminog *et al*. and Wilzén *et al*. noted in their reviews that the risk of some malignancies tended to be higher in patients with SCD.[13,36] In their conclusions, the authors suggested the need for further studies at genetic and molecular levels to determine the basis for such risk.

Of note in the index case is that the presenting complaint of abdominal distension and pain are identical to the usual clinical features of SCD and so were attributed to the latter for a very long time until the abdominal mass was well advanced. This also holds true for most of the other features of cancers such as jaundice, anorexia, weight loss and bone pains, all of which may delay a thorough evaluation for cancer in an SCD patient. Asa *et al*. in their study reported the findings in paragangliomas located in unusual locations and suggested a high index of suspicion coupled with thorough examination and investigations.[37]

CONCLUSION

Several reports strongly suggest an altered risk of cancer in SCD through genetic and epigenetic mechanisms. Over time, more research will validate or disprove this finding and shed more light on the range of cancers involved, especially those with strong underlying genetic basis like paraganglioma. The extensive overlap of symptomatology between SCD and intra-abdominal cancers will also receive greater attention so that the index of suspicion for possible cancer in the SCD patient will be raised.

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Conflicts of interest
There are no conflicts of interest

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