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EBV-Positive Grey Zone Lymphoma in an HIV Infected Man from Kampala, Uganda: Case Report

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Authors' contributions

This work was carried out in collaboration with all authors. Author LKT provided the case and wrote the draft manuscript. Author JO provided the detailed patient case notes and managed the literature searches and author LWA designed the figures, managed the literature searches and contributed to correction of the draft. All authors read and approved the final version of the manuscript.

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Case Study

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ABSTRACT

Aim: We describe the clinical, histopathological and immunophenotypic characteristics of an HIV-infected adult man on antiretroviral therapy who presented with an EBV-positive grey zone lymphoma.
Case Presentation: A 56-year-old HIV infected man from Uganda presented with a four month history of progressive abdominal swelling and B-symptoms. He was on highly active antiretroviral therapy (HAART) and cotrimoxazole. He was afebrile (36.9℃), severely wasted (BMI 14.8), and mildly anaemic. On physical examination, he had a 15 by 8 cm mass in the hypogastrium and umbilical region.
The total white cell count was $8.3X10^3$/μL; neutrophils, $5.72X10^3$/μL; haemoglobin 11.1g/dL,

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platelets 528X10^3/µL, LDH 197 IU/L and CD4 367/µL. Abdominal ultrasound and CT scan showed a tumour involving the mesentery, jejunum and mid ileum. At laparotomy, a biopsy was taken, fixed, processed and stained with Haematoxylin & Eosin (H & E). Histopathology demonstrated large pleomorphic cells admixed with inflammatory smaller cells, Reed-Sternberg-like cell variants and frequent abnormal mitoses. Biomarkers CD20, PAX5, CD30 were positive but ALK negative (immunohistochemistry and strong EBER positivity in situ hybridization. The patient improved on modified CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy.

Discussion: The tumour had features intermediate between mediastinal large B cell lymphoma and classical Hodgkin lymphoma.

Conclusion: We present a case of EBV-positive grey zone lymphoma in an HIV-infected man on HAART therapy diagnosed and treated in a resource constrained medical setting. The histological features are unusual and represent a low incidence lymphoma that is recognized by mixed features reminiscent of Hodgkin's lymphoma and mediastinal large B-cell lymphoma.

Keywords: HIV/AIDS; EBV; grey zone lymphoma; Uganda.

1. INTRODUCTION

In most low income countries of Africa, especially sub Saharan Africa, lymphomas are diagnosed using morphology alone [1]. The diagnosis of lymphoma in developed countries is currently based on morphology, the patient's clinical data, immmunophenotype and molecular studies.

The 2008 WHO classification recognizes a group of lymphomas that do not fit in any of the clearly defined categories: "the grey zone lymphomas" [2]. These present a diagnostic dilemma due to the presence of overlapping clinical, morphologic, immunophenotypic and molecular features of two well defined groups [2,3].

Most common of the grey zone lymphomas are the "B cell lymphoma unclassifiable between diffuse large B cell lymphomas (DLBCL) and classical Hodgkin lymphoma (cHL)". They are mainly mediastinal although several recent studies have shown that they may present in extramediastinal locations as well. These tumors are usually clinically aggressive [4-6].

Primary mediastinal B-cell lymphomas (PMBL) display morphologic and immunophenotypic features similar to those of classic Hodgkin lymphoma (cHL). For this reason they are called "mediastinal grey zone lymphoma" or "large B cell lymphoma with Hodgkin features" [4,7,8].

Accurate diagnosis and characterization of these tumors is essential to enable specific treatment and prognosis [9]. EBV positive grey zone lymphomas in HIV infected patients have been rarely reported [10]. Grey zone lymphomas display features similar to primary mediastinal B cell lymphoma and classic Hodgkin lymphoma [2]. In particular, there is a diffuse pattern of large round, oval or polygonal cells, with bizarre pleomorphic nuclei: some resembling Hodgkin and/or Reed-Sternberg cells and tumor cells of anaplastic large cell lymphoma (ALCL) [11].

Most large B cell lymphomas presenting in immunocompromised patients are EBV positive. EBV is thought to contribute to lymphomagenesis through promotion of B cell proliferation. On the other hand, the contribution of HIV to lymphomagenesis is complex but it is thought to be through immunodeficiency and molecular lesions [12]. Co-infection with oncogenic viruses such as HHV8 and Epstein-Barr virus (EBV) might also contribute [13]. A distinct category of DLBCL that occurs in the elderly patients, that is 'EBV-positive diffuse large B cell lymphoma of the elderly' has also been rarely identified [14]. We report a case of EBV-positive grey zone lymphoma in an HIV infected adult male from Kampala, Uganda.

2. CASE PRESENTATION

A 56-year-old HIV infected African man from Kampala, Uganda presented to our hospital with a four months history of progressive abdominal distension, drenching night sweats, evening fevers, poor appetite and weight loss. He did not vomit; have constipation, abdominal pain or diarrhoea. He had been receiving highly active antiretroviral therapy (HAART) and co-trimoxazole prophylaxis for *Pneumocystis jiroveci*.

This was his second admission to hospital. He had been hospitalised for the same condition a month earlier, before being referred for further management. During the previous admission in a

secondary health care setting, an exploratory laparotomy was done and the colon was found nested together forming a mass anterior to the aorta. The abdomen was closed and the mass left intact. He was then referred to our hospital.

He was married with two children. He was a retired soldier and a peasant farmer. There was no history of diabetes, hypertension or sickle cell disease in the family. He did not take alcohol neither smoke tobacco nor cigarettes.

On examination, he was a middle aged man, with an axillary temperature of 36.9℃. He was severely wasted (weight: 46kgs, height 176.5 cms and BMI of 14.8) had mild anaemia and no jaundice. He had lipodystrophy of the face and dark patches on his finger nails.

He had a midline sub umbilical surgical scar on his abdominal wall with a tender pulsatile mass in the hypogastrium and umbilical region extending 4 cms to the epigastrium. It measured 15 cms by 8 cms, the overlying skin was irregular and attached to the base. There was no bruit, however, and the bowel sounds were increased. Rectal examination was normal. The respiratory, cardiovascular, musculoskeletal and the central nervous systems were essentially normal.

Results of laboratory tests included: total white cell count (WBC) of $8.3X10^3/\mu L$. Neutrophils, $5.72X10^3/\mu L$. Haemoglobin 11.1g/dL and platelet count $528X10^3/\mu L$. Liver and renal function tests were normal. Lactate dehydrogenase was 197 IU/L. The chest X-ray and echocardiography (ECHO) were normal, but the electrocardiogram (ECG) revealed sinus bradycardia. The nadir CD4 T cell count was 0.26/µL five years prior to admission in our hospital when he was started on HAART. On admission, he had last had his CD4 T cell count done two years prior and it was 351/ µL. At admission, the CD4 T cell count was 367/µL.

Ultrasound examination of the abdomen confirmed the presence of a mass and at CT scan, there was a midline intra-abdominal mass lesion that arose from above the aortic bifurcation and slightly below the origin of the inferior mesenteric artery and extended to the pelvic cavity. It was anterior to the aorta and did not involve it as well as the lower portion of the superior mesenteric artery. It involved the mesentery. It was heavily vascularised. These features were suggestive of a neoplastic mesenteric tumour with small bowel involvement. A laparotomy revealed a mesenteric tumour involving the mesentery at the level of the mid ileum.

Cytopathological examination done during the operation was suggestive of lymphoma. A biopsy was taken for further histopathological work up.

Histopathology of prepared tissues stained by (H & E) revealed a population of very large pleomorphic cells suggestive of Reed-Sternberg cells and admixed with smaller inflammatory cells. These Reed-Sternberg like variants, with abnormal mitoses. A provisional diagnosis of anaplastic large cell lymphoma was made. Immunohistochemistry was carried out at the Department of Pathology, Ohio State University, Columbus, Ohio revealed that the large pleomorphic cells were CD20+, PAX5+ and CD30+ but ALK negative. The tumor cells were large or medium and were strongly EBER+. The small background cells were CD3 positive. All these features were suggestive of an EBV positive large B cell lymphoma, with Hodgkin features.

The patient was initially rehydrated with normal saline and 5% dextrose. He later received allopurinol and the first course of chemotherapy after stabilisation. This included modified CHOP: cyclophosphamide 750 mg/m^2, Doxorubicin $50mg/m^2$ and Vincristine 1.4 mg/m^2 on day one and prednisolone 100 mg on days one to five, repeated every 21 days. He registered satisfactory progress, and is alive and well.

3. DISCUSSION

This patient's tumor had clinical, histopathological features and immunophenotype intermediate between mediastinal large B cell lymphoma and classical Hodgkin lymphoma. It was located in the mesentery at the level of the mid ileum.

Histomorphologically, there was a diffuse pattern of very large pleomorphic and anaplastic cells admixed with smaller mature lymphocytes, Reed-Sternberg-like variants, with plenty of abnormal mitoses and an inflammatory cell background. These features are similar to those of mediastinal large B cell lymphoma which presents with features of medium sized to large cells with abundant pale cytoplasm and more or less round or ovoid nuclei. In some cases, lymphoma cells had pleomorphic and/or multilobated nuclei which resembled Reed-Sternberg cells hence

raising the suspicion of Hodgkin lymphoma or Anaplastic large cell lymphoma (see Fig. 1) [15]. The majority of the tumors reported in the literature are located in the mediastinum, however there are a few that are extramediastinal like in our patient who had a mesenteric tumor [4,5].

Immunohistochemically, the tumor expressed mature B-cell markers; positive for CD20, CD79a, PAX-5 (see Fig. 1). This is similar to the immunophenotype of mediastinal large B cell lymphoma with expression of B-cell antigens and lack of surface Immunoglobulins [16].

CD30 was expressed especially by the Hodgkin-like, Reed-Sternberg cells. This has been seen in similar cases where the expression of CD30 is heterogeneous with weak to strong intensity [5]. These features are similar to those of classical Hodgkin lymphoma.

CD15 and CD10 were weakly expressed, but ALK was negative. Activated B-cell markers like MUM-1 were strongly expressed as well, and EBER was strongly positive. EBV is usually associated with classic Hodgkin lymphoma (cHL) but not primary mediastinal large B cell lymphoma (PMBL). However, most AIDS related lymphomas are strongly associated with EBV. The presence of EBV and Hodgkin-like cells also raised the possibility of an EBV positive large B cell lymphoma in the elderly. Most of the reported gray zone lymphomas are not EBV positive [17].

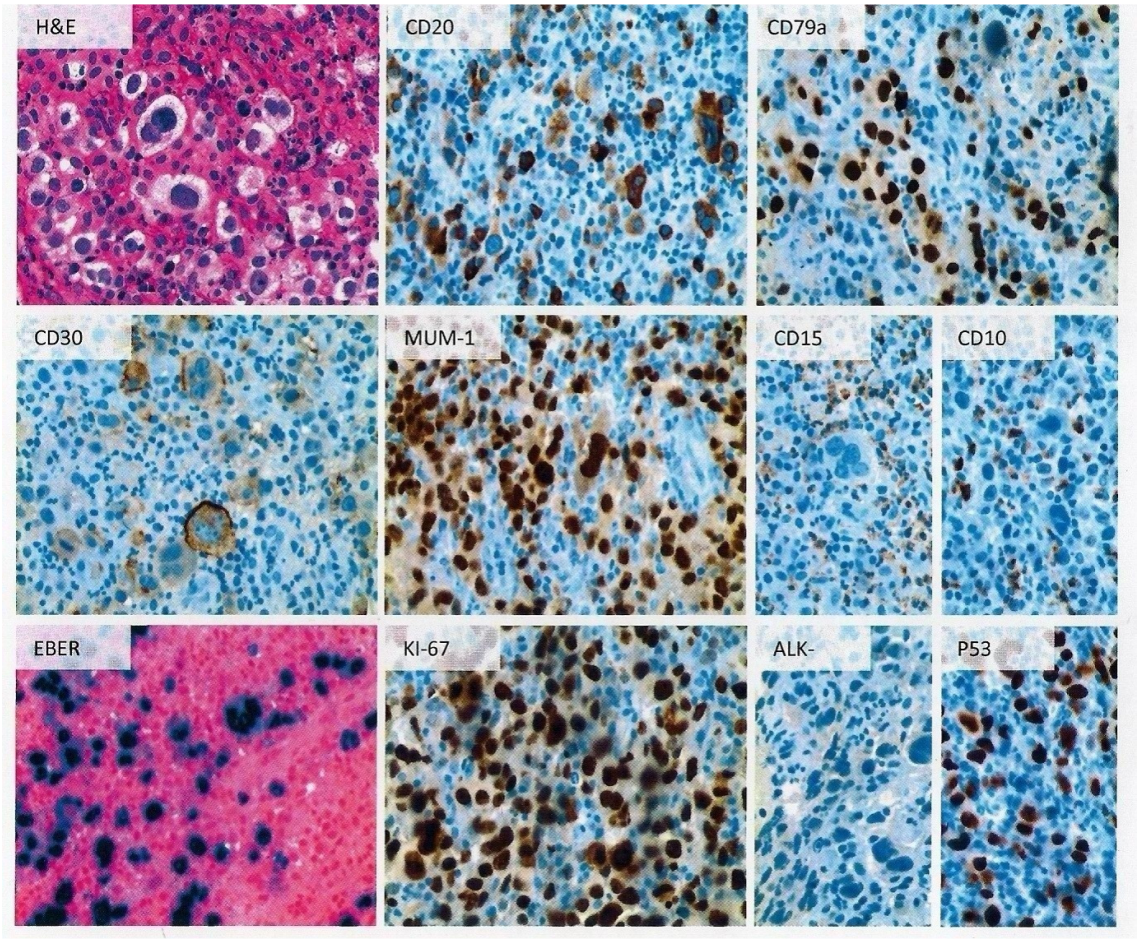

Fig. 1. At light microscopy, under Haematoxylin and Eosin staining (H&E) a population of very large bi-nucleated and multinucleated cells admixed with smaller cells, Reed-Sternberg- like variants and plenty of abnormal mitoses which turned out to be CD20+, CD79a+, CD30+, MUM-1 positive, CD15-, CD10-, EBER+, Ki-67>80%, ALK- and P53+. Based on these findings we made a diagnosis of grey zone lymphoma

In the current literature, there is only one report of an EBV positive gray zone lymphoma in an elderly female who was not HIV infected[8]. Although our patient was above 50 years, the diagnosis of EBV positive large B cell lymphoma in the elderly was excluded because there was a known cause of immunodeficiency which was HIV/AIDS infection. EBV+ DLBCL in the elderly has been described in patients who are more than 50 years of age with no known cause of immunodeficiency. Bhattacharya has also described cases of Hodgkin lymphoma in patients on combined antiretroviral therapy (cART), and an increased prevalence of Hodgkin lymphoma in the cART era as compared the pre-cART era. This prevalence increased with CD T cell count [18]. However, in our patient the clinical, morphological and immunophenotype was not specific to any of the distinct groups, classic Hodgkin lymphoma and mediastinal large B cell lymphoma, hence the diagnosis of gray zone lymphoma. Our patient's immunophenotype was (strong B-cell immunophenotype CD20+, CD79a+, PAX-5, CD30+, CD15+/-, CD10+/-, ALK- and EBER+) which does not fit in the description for Nodular sclerosis Classic Hodgkin lymphoma with weak B-cell antigen expression (CD20- is weakly or variably expressed and PAX-5 and CD79a are weak or negative, CD30+, CD15+, CD10-, ALK- and EBER+) and primary mediastinal B cell lymphoma (CD20-, CD15+….

The most recent 2008 WHO classification recognizes a group of lymphomas that do not fit in any of the clearly defined categories: "the grey zone lymphomas" which present a diagnostic dilemma because of the presence of overlapping clinical, morphologic, immunophenotypic and molecular features of two well defined groups [2,19]. This classification gives the histopathologist 'the opportunity, to assign these lymphomas to a designated group' that has features of large B cell lymphomas and Hodgkin disease.

Our patient was treated with the regimen for aggressive B-cell non Hodgkin lymphoma and highly active antiretroviral therapy (HAART). He did very well on this treatment and completed all the six cycles of therapy. This is in line with what most recent studies have recommended that these tumors are treated using therapy for aggressive B-cell non Hodgkin lymphomas. Clinical trials have not been realized due to the rarity of this type of tumor and the lack of uniform diagnostic criteria for the Mediastinal grey zone lymphomas. The recommended treatment for grey zone lymphomas is CHOP-like regimens [20,21]. The patient described in this report hence presents with features suggestive of grey zone lymphoma in an HIV positive patient. It remains to be seen whether such patients should be classified solely as grey zone lymphomas or whether they should be assigned to their own category.

4. CONCLUSION

This was a case of HIV/AIDS-related EBV-positive grey zone lymphoma in an adult male from Kampala, Uganda. It was a malignant lymphoma with histological features and immunophenotype intermediate between mediastinal large B cell lymphoma and classical Hodgkin lymphoma. Use of immunohistochemistry in the classification of NHL is vital, without which the specific subtypes are very difficult to classify.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and its accompanying images.

ETHICAL ISSUES

This case study was part of a larger study of the Mid- Region Aids and Cancer Specimen Resource and Sub Saharan Lymphoma Consortium (SSALC) Uganda study NIH Grant number U01 CA 06652. Ethical approval was sought from the Institutional Review Board protocol number REC REF 2009-093.

Further written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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