NON HOGDKIN LYMPHOMA ASSOCIATED WITH SCHISTOSOMAISIS? A CASE REPORT AND THE SIGNIFICANCE OF TUMOUR MARKERS

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Abstract
We report a case of a possible association of schistosomiasis with Non-Hodgkins lymphoma. A 19 year old Nigerian lady presented with week long history of abdominal swelling and vomiting. Sonography of the abdominal cavity gave a diagnosis of colonic tumour. Resected portion of the ileum showed an ileoceacal mass appearing like an intususception. Histopathology initially revealed schistosomal ova and the adult worm in-copula, Immunohistochemistry however revealed that the mass was not just a granuloma, but a diffuse B-lymphocyte Non-Hodgkins lymphocytic lymphoma. The proximity of the schistosoma ova in the tissue sections suggests that schistosomiasis may have some effect on carcinogenesis. We therefore recommend that patients with chronic parasitic infestation, especially schistosomiasis, should be monitored more closely in view of the relevant emerging association between cancer and infections.
Keywords: schistosomiasis; Non-Hodgkins lymphoma; colonic tumour

1. Introduction

Schistosomiasis is a fairly prevalent communicable disease in the tropics and subtropics caused by a trematode of the genus schistosoma. It affects more than 200 million people worldwide, with over 700 million living under conditions favourable to transmission [1]. In endemic areas, schistosomal infestation has been implicated in the aetiology of several human malignancies including bladder, liver and colorectal cancer[2]. Many papers have been published about colorectal carcinoma cases associated with *S. japonicum* infection [3], but it remains to be determined whether this association is significant or not[4]. The association between schistosomiasis and lymphomas is far less reported. A case of hepatosplenic schistosomiasis associated with histiocytic lymphoma was reported and concluded that schistosomiasis may be related as a causative factor for the malignant disease[5&6]. Chronic intestinal schistosomiasis presenting in a previously asymptomatic 34-year old woman from Saudi Arabia with large B cell lymphoma was reported. The patient presented with abdominal pain, constipation, recurrent rectal bleeding and persistent mild eosinophilia during chemotherapy, while stool samples were repeatedly negative for parasite ova. Another article reported a case malignant lymphoma coexisting with *S. japonica* infection in a man who had experienced general malaise for one month, presenting to a hospital with abdominal pain, distention and vomiting. It is hypothesized that the relationship between *Schistosomiasis* and cancer has much in common with that between *Helicobacter pylori* and mucosa-associated lymphoid tumours, and that between Epstein-Bar virus and lymphomas in that the mechanisms of chronic inflammation act as cancer-promoting factors. They further reported that lymphoma cells proliferated around egg emboli in Glisson's capsule and portal vein branches, suggesting a close relationship between the infection and the lymphoma [7]. Recent advances in the field of molecular Biology and epidemiology have led to significant revelations to clarify the relationship between the infectious agents and cancer and have given valuable insights into the molecular basis of carcinogenesis. Infections in general can initiate or promote carcinogenesis by any of the three main mechanisms: chronic inflammation due to persistence of infectious agent in the host with the release of reactive oxygen radicals and reactive nitrogen radicals having the potential to damage DNA; insertion of active oncogen in the host genomes (mechanism associated with

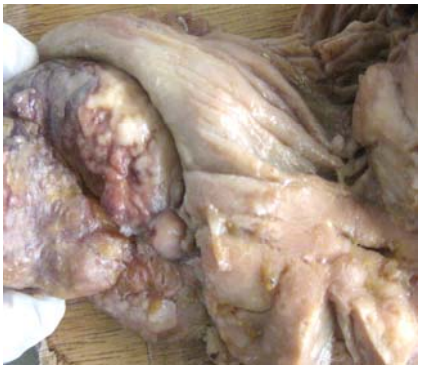
oncogenic virus as hepatitis B virus [HBV]; and reduced immunesurvellance as a result of immunosuppression[7].

2. Case Report

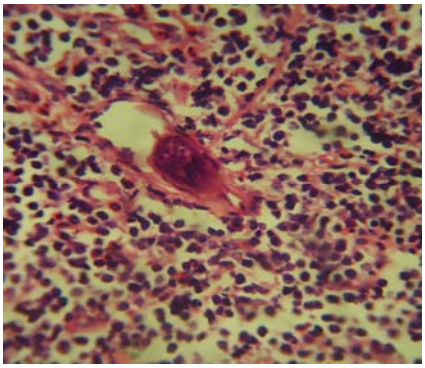
We report the case of a non Hodgkin lymphoma in association with *Schistosoma mansoni* infection because this is considered rare. This 19year old female patient who lives in the low lands adjourning the Jos plateau was first seen with a week long history of abdominal swelling and vomiting. She had a first exploratory laparotomy in a private hospital for an ileoceacal volvulus three prior to presentation. She did well for a while until a week prior to presentation when she started having progressively enlarging abdomen associated with projectile vomiting and weight loss. Clinical examination gave impression of recurrent intussusception but the cause was not known. The laboratory tests requested were urinalysis, PCV and blood group which clearly showed that a lymphoma was not envisaged. Ultrasound scan revealed an echogenic mass measuring 8.2cm x 8.3cm posterior to the uterus and a mild peritoneal collection. The diagnosis from the USS diagnosis was colonic tumour. At surgery, an ileoceacal mass was excised for histopathology. The resected ileoceacal mass measured 24x4cm (Fig A), while the mass in the lumen of the gastro intestinal tract measured 10x10x8cm and together with the resected portion of the GIT weighed 650g. The Histopathology diagnosis in the first instance, was schistosomiasis as indicated in (Fig.B-D), with worrisome histologic features around the ova which was interpreted as severe inflammatory reaction with cellular infiltration. The patient was subsequently treated with Praziquantel along with antibiotics and metronidazole. The patient reported improvement which lasted about four months but soon had a full relapse of the original symptoms. We decided to stain sections of the tumor using immunohistochemical methods with the following antibodies/tumour makers CD20,LCA,Ki67,p53,CD3,CD34,Ckit and EMA) and this was positive for non-Hodgkin's lymphoma.(table 1, Figs E-H.) We then revisited the Haematoxylin and Eosin method and noticed the missed diagnosis. The second reading of the histology slides revealed sheets of neoplastic lymphocytes exhibiting hyperchromasia, high nucleo-cytoplasmic ratio with granular nuclei infiltrating the colonic muscle layer. Thick walled blood vessels were also observed. We made several efforts to invite the patient back for treatment and follow up by the haematologist but to no avail because the relatives of the patient believed that the problem was spiritual and therefore needed a spiritual solution. Eight months later, the patient died.

Table 1:

Antibodies used	Makers for	Reactive	Non reactive
Cluster of Differentiation 20(CD20)	B-cell Lymphoma	+ve	
Luekocyte common Antigen(LCA)	Lymphoma	+ve	
Kiel 67(Ki67)	Proliferative tumour maker	+ve	
Tumour Protien 53(p53)	Regulatory apoptotic protien	+ve	
Cluster of Differentiation 3(CD3)	T-cell Lymphoma		-ve
Cluster of Differentiation 34(CD34)	Stromal		-ve
Ckit	GIST		-ve
Epithelial membrane Antigen(EMA)	Carcinomas of epithelial origin		-ve



A



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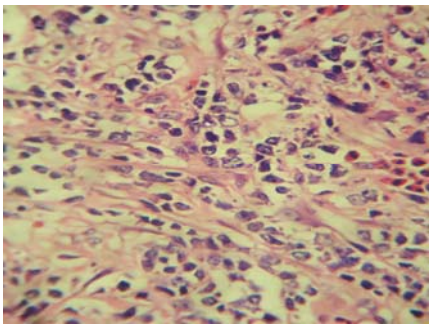

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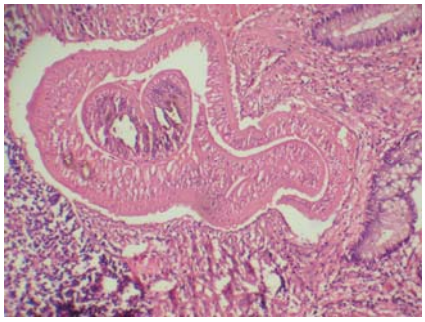

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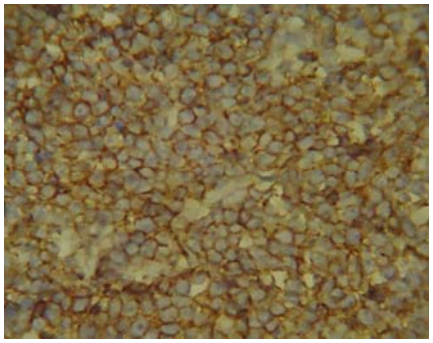

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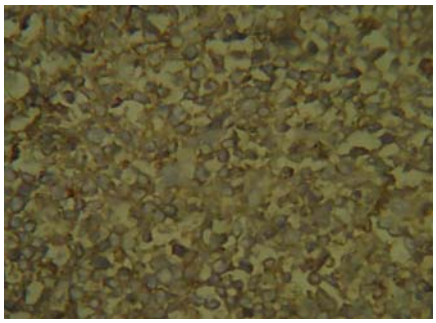

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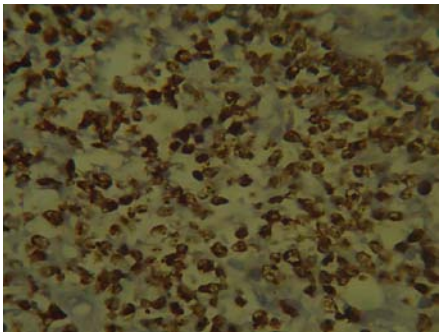
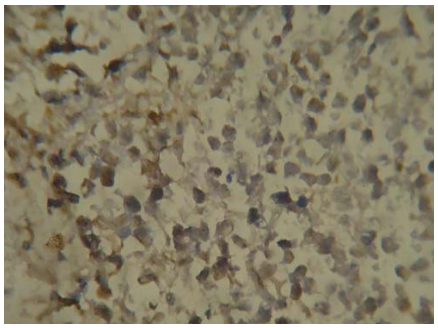


G



H

Fig.A: Lumen of the Gastrointestinal Tract; B-Large nodular mass obstructing the intesting(X160).

Fig.B: Section o Schistosome egg surrounded by diffuse sheets of lymphocytes with pleomorphic, hyperchromatic nuclei with little or no cytoplasm. DIFFUSE LYMPHOCYTIC LYMPHOMA (x640)

Fig.C: Histologic section showing lymphocytes with pleomorphic, hyperchromatic nuclei with little or no cytoplasm. At the right hand side of the section are clusters of eosinophils (arrow)x640.

Fig.D: Histologic section of Gastrointestinal tract showing adult schistosome in copula.on the right hand side of the parasite are glandular epithelia and to the left hand side a cluster of lymphocytes (x160)

Fig.E: Cluster of Differentiation 20(CD20) reactive section indicating B-cell diffused Non-Hodgkins Lymphocytic Lymphoma. Cell membrane reaction is obvious as a dark brown coloration in many cells. The nuclei are stained light blue in the haematoxylin conterstain.(x 640)

Fig.F: LCA reactive section indicating B-cell diffused Non-Hodgkins Lymphocytic Lymphoma. Cell membrane reaction is obvious as a dark brown coloration in many cells. The nuclei are stained light blue in the haematoxylin conterstain.(x 640)

Fig.G: Ki67 immunostaining of Lymphnode tumour showing fractions of Ki-67 highly positive tumour cells (brown). (x 640)

Fig.H: A micrograph showing cells with abnormal p53 expression (brown) in a Lymphnode tumour. P53 immunostain.(x640)

3. Discussion

The schistosome parasite is a flat, digenetic blood-dwelling fluke which has a definitive mammalian host and an intermediate snail host. The adult worm of *S. mansoni* are found in copula in the mesenteric vessels where they lay there eggs. The eggs penetrate the intestinal wall

and are shed in the stool of the human host. Upon contact with fresh water, the eggs hatch and release miracidia which, after infecting the appropriate snail host multiply asexually into cercariae. Following penetration of the human skin, the cercarial lavea transform into schistosomulae and undergo maturation in the portal vein. The mature male and female worms typically mate and inhabit the mesenteric venules. Eventually, gravid female worms release eggs which traverse the intestinal wall to reach faeces and renew the cycle. Many ova are however retained in the intestinal wall, particularly the rectum, or flow backward and cause egg embolism in the liver and other organs. In the intestine, the sequestered eggs in the mucosa and submucosa incite a severe inflamatory reaction with cellular infilteration and consequent granuloma formation. This in turn leads to mucosal ulceration, microabcess formation, polyposis and various neoplastic transformation[8] .

The symptoms presented by this patient, except for abdominal pain, are not consistent with the classical presentations of acute and chronic presentations which have been well described [9,10,11,12&13] . These include vomiting, progressive enlargement of the abdomen, weight loss, sustained fatigue and mild peritoneal fluid collection. Abdominal tuberculosis, appendical mass, abdominal lymphoma and chronic inflamatory bowel diseases are all differential diagnosis of this case. The ultrasound scan however revealed a colonic mass and at surgery was found to be an ileoceacal mass which was resected for histopathology. The diagnosis of schistosomiasis from this biopsy siting both ova and the adult worm gave the impression that the excised mass was merely a huge granuloma which is normally expected. This was the basis of the initial diagnosis. However treatment for schistosomiasis using praziquantel is ordinarily known to be an effective specific antiparasitic therapy and has been well documented[14&15] . The relapse of symptoms a few weeks after treatment was therefore the first indication to some other cause to the symptoms.

Epidemiologic studies of the association of *S. japonicum* and colorectal cancer incidence and mortality have been severally reported especially in China and Japan[16,17,18,19&20] . However epidemiological evidences associating *S. mansoni* infection and colorectal cancer is either lacking, of poor quality or conflicting[21]. Supporting the absence of such a causal association, Parkin pointed out that although there is a great disparity in the geographical distribution of *S. mansoni*, colorectal cancer occurs in the African continent with clear uniformity[22].

There is however great paucity of information about the association between *S. mansoni* and lymphoma and hence the need and justification for this case report. The exact etiopathogenesis of lymphoma associated with *Schistosomiasis mansoni* is difficult to understand and several explanations have been advanced not just for this, but for the association between other malignancies and schistosomiasis in general. These include: the presence of endogenously produced carcinogens [23] , chronic immunomodulation resulting in impairment of immunological surveillance [24] , symbiotic action of other infective agents [25] , and the presence of schistosomal toxins [26] . While these factors may interact to induce carcinogenesis, chronic inflammation appears to play a central role [21]. It has been suggested that chronic inflammatory reaction provoked by schistosome antigens provides the proliferative stimulus necessary to promote cancer growth from potentially malignant foci produced by other carcinogens[27] . Inflammatory cells generate potentially genotoxic mediators during the course of schistosomal infection such as reactive oxygen and nitrogen species and proinflammatory cytokines which cause genomic instability and dysregulation of oncogens and oncosuppressor genes[28 & 29].

The use of IHC in this study underscores the importance of tumour markers in diagnosis. The CD antibodies enabled in the specific diagnosis of B-cell Lymphoma. Although this is most useful in differentiating diffuse large B-cell lymphoma(DLBCL) from anaplastic large cell lymphoma(ALCL) for the purpose of better treatment and prognosis, it has enabled precise diagnosis of lymphoma in this study. The positive reactions obtained with the Ki67 and P53, both support the diagnosis of a tumour. The Ki67 antigen is exclusively detected within the cell nucleus and is associated with and may be necessary for cellular proliferation. The positive reaction obtained is therefore consistent with the CD20 positive reaction for B-cell Lymphoma. The antibody is an excellent marker that determines the growth fraction of a given cell population. The P53 is a tumour suppressor protein that in humans regulates the cell cycle and thus functions as a tumour suppressor that is involved in preventing cancer. P53 has several mechanism of anticancer function and plays a

role in apoptosis, genomic stability and inhibition of angiogenesis.

The negative reactions of CD3, CD34, Ckit and EMA have complemented positive reactivity with CD20, LCA, Ki67 and P53 for specific diagnosis of lymphoma. Although IHC was not originally planned for this study, the findings in this case report have clearly brought out the place IHC in the accurate histopathologic diagnosis of diseases especially against a backdrop of confusing signs and symptoms. While this report may not be able to prove the part of schistosomiasis in the pathogenesis of lymphoma, it is a further addition to the number of literature that suggest an association between chronic schistosomiasis and neoplastic changes

Conclusion:

This study further highlights the significance of immunohistochemistry in the practice of Histopathology and the potentials to improve accuracy in diagnosis and revolutionize medical practice especially in the under developed world. It also shows that patients with chronic parasitic infestations, which is very common in our environment, should be monitored subsequently for tumours because of this relevant emerging association between cancer and infections.

Informed consent

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

The authors declare that they have no competing interests.

Authors' Contributions

JOA conceived and designed the report and wrote the initial manuscript, ECE performed the literature search, photomicrography and contributed to writing the manuscript. JUM prepared the protocols for the immunohistochemistry and stained the slides. OAS, GOE and JOA examined the Haematoxylin and Eosin stained slides, while JOA, ECE and JUM interpreted the immunohistochemistry. FJG and JMC are the clinicians that obtained all clinical information, read through the manuscript and secured the needed informed consent and ethical clearance. AYB processed the tissue and prepared the histology slides and read through the manuscript for technical accuracy. All authors read and consented to the final manuscript.

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