East African Medical Journal Vol. 96 No. 2 February 2019
A RARE CASE OF MALIGNANT PHYLLOIDES TUMOUR OF THE BREAST IN NEUROFIBROMATOSIS TYPE 1: NOT JUST A SPORADIC OCCURRENCE?
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A RARE CASE OF MALIGNANT PHYLLOIDES TUMOUR OF THE BREAST IN NEUROFIBROMATOSIS TYPE 1: NOT JUST A SPORADIC OCCURRENCE?

A. O. Wamalwa, E. S. Miima and J. W. Githaiga

SUMMARY

Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystem disorder that predisposes to rare malignancies. Performing molecular studies in Neurofibromatosis type 1 (NF1) patients may prove useful in determining susceptibility to these malignancies. We describe a rare case of a twenty-two (22) year old woman with NF1 presenting with malignant phylloides of the breast. Due to paucity of guidelines, we describe challenges encountered during management.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystem genetic disorder resulting from a mutation in or deletion of the NF1 gene with effects on skin, skeletal and nervous systems. NF1 predisposes patients to particularly rare tumors which could be both benign and malignant. The occurrence of malignant phylloides of the breast is extremely rare hence the paucity of evidence-based management guidelines (1). We describe a case of malignant phylloides of the breast in a patient with NF1 and explore the possibility of genetic susceptibility. We also outline diagnostic challenges as well as review management options.

CASE REPORT

A twenty-two year (22) old female patient presented to the general surgical unit at Kenyatta National Hospital (KNH) with a sixteen (16) month history of right breast swelling. The swelling was initially painless and progressively increased in size before it ulcerated and resulted in a painful hemorrhagic-purulent wound over the immediate seven (7) months. There was associated weight loss, fever, dizziness and fatigue. She also had multiple painless skin lesions on her torso, which had been present since childhood and were not increasing in number and size. There was no known family history of similar skin lesions. There was no

associated axillary swelling, no prior history of radiation to the chest, no personal or family history of breast disease or breast cancer. She was nulliparous, had menarche at fifteen (15) years and experienced a regular menstrual cycle. She had no history of hormonal contraceptives, no history of smoking cigarettes or consuming alcohol. She had sought alternative medical therapy which included use of oral and topical herbal medication.

On general examination, she was pale, in poor nutrition, not jaundiced with absent palpable lymph nodes. She was febrile (37.3^0C) with a normal pulse rate and blood pressure. Right breast examination showed a 25cm by 20cm tender mass foul smelling, ulcerated with purulent discharge, which was fixed to adjacent skin with no palpable axillary nodes, the left breast was normal. She also had multiple cutaneous and subcutaneous non tender nodules of varying sizes (2 – 4 cm), distributed on her forehead and torso, and with multiple hyper pigmented macular lesions on her torso. Further systemic examination was normal.

She had been reviewed at a peripheral health facility where a breast ultrasound done two months after onset of the symptoms indicated a 7.26cm by 4.6cm mixed echogenic right breast mass with no axillary adenopathy and a mammogram one month later reported a well circumscribed lesion with well-defined margins on the right breast. Abdominopelvic ultrasound showed simple right ovarian cyst, chest radiograph was normal. Fine needle aspirate and cytology (FNAc) indicated smears composed of crowded groups of round to spindle shaped cells. Conclusion made was of a stromal proliferative lesion with various ductal proliferation compatible with a benign phylloides tumor.

In our unit, the complete blood count showed leukocytosis, neutrophilia, microcytic anemia and reactive thrombocytosis. The renal function tests were all within normal ranges. Liver function test showed low albumin and elevated aspartate transaminases. A Human Immunodeficiency Virus (HIV) rapid test was negative. The tumor had ulcerated which was not in keeping with benign tumor hence a request for incisional biopsy was made. Histopathology reported sheets of malignant mesodermal tumor that has ulcerated the overlying skin, marked pleormorphism, multinucleate cells in a background of myxoid stroma with spindle cells in the background. Conclusion made was a malignant peripheral nerve sheath tumor.

She was put on intravenous antibiotics, analgesics and the anemia corrected. Simple mastectomy was performed (Image 1) and patient discharged on post-operative day five with a clean dry wound via breast clinic and neurology clinic. The patient declined to have a breast reconstruction. No adjuvant treatment was provided. Histopathology of the breast specimen indicated malignant phylloides tumor confirmed by Immunohistochemistry of which was CD117 positive, S100 negative, epithelial staining on Cytokeratin, Ki67 was 40-50% (Figures 1-6) and margins were negative for tumor. Follow up review at two years revealed no clinical features of recurrence.

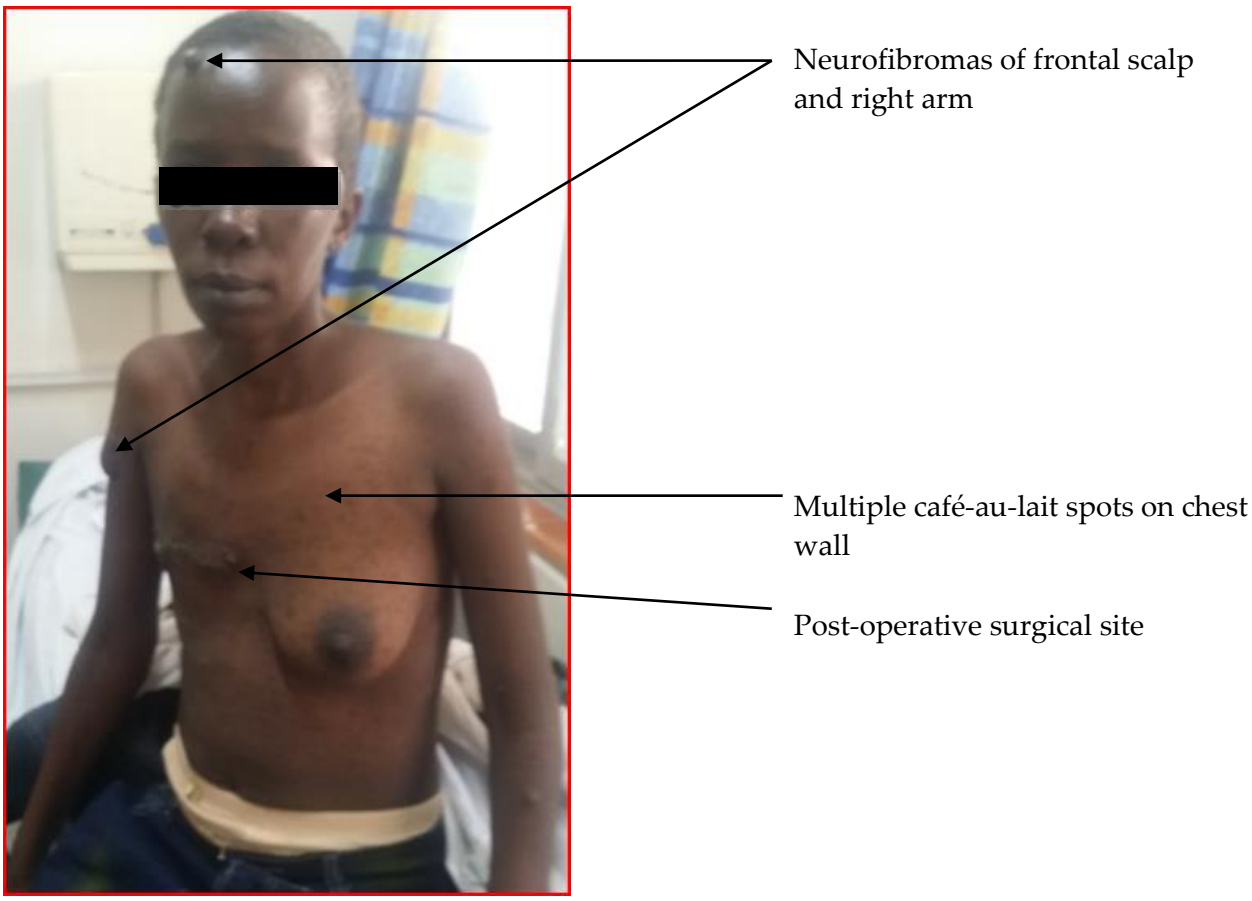

Image1: Neuofbromas on scalp and right arm illustrated. Multiple café-au-lait spots on chest wall illustrated. Post-operative appearnce of the surgical site ialso illustrated.

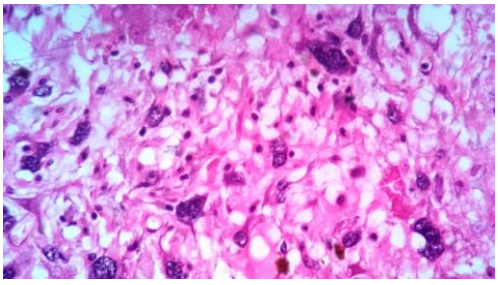

Figure 1A

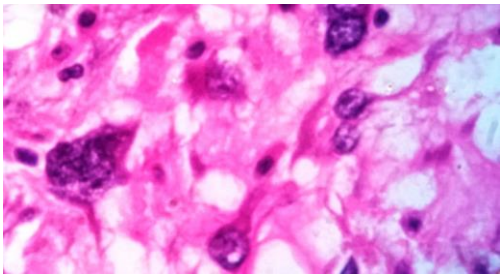

Figure 1B

Figure 1: An intermediate (1A) and high (1B) power view of routine hematoxylin and eosin (H&E stain) illustrating malignant spindle cell.

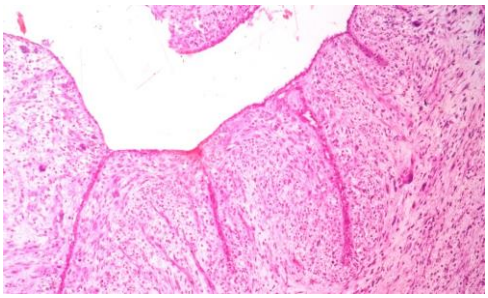

Figure 2A

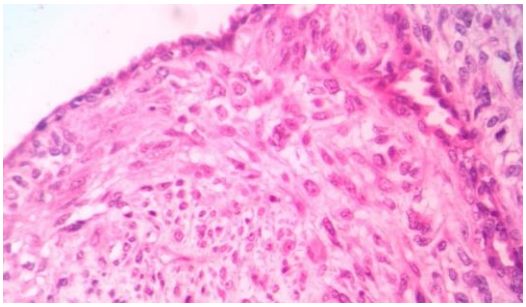

Figure 2B

Figure 2: An intermediate (2A) and high (2B) power view of routine hematoxylin and eosin (H&E stain) illustrating benign epithelial glands.

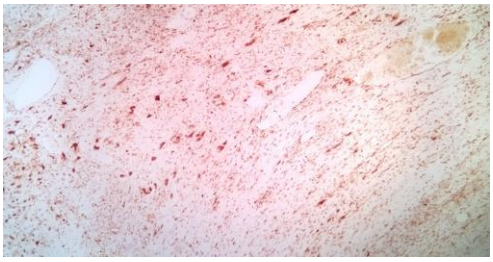

Figure 3A

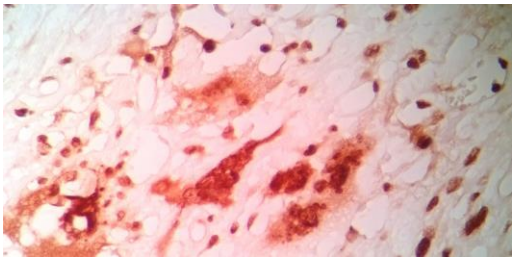

Figure 3B

Figure 3: A low (3A) and high (3B) power view illustrating immune-reactivity for CD117

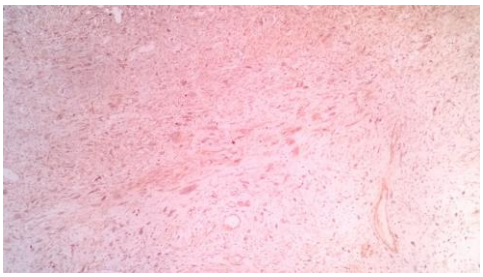

Figure 4A

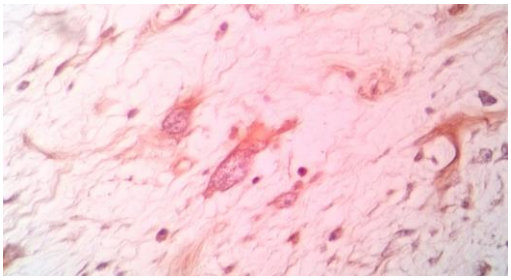

Figure 4B

Figure 4: A low (4A) and high (4B) power view illustrating negative staining for S100

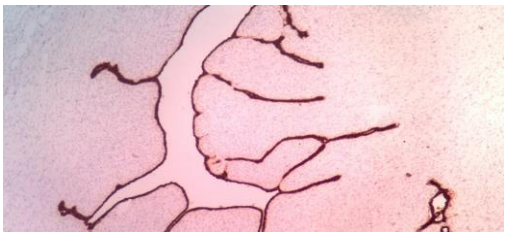

Figure 5A

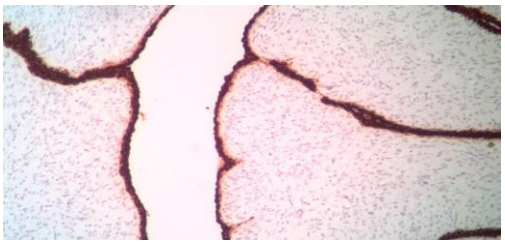

Figure 5B

Figure 5: A low (5A) and intermediate (5B) power view illustrating CK-epithelial gland staining

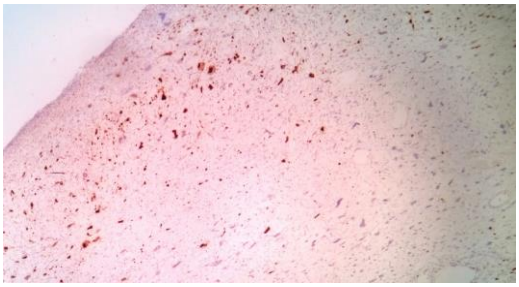

Figure 6A

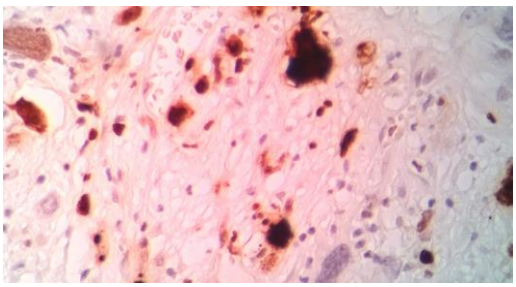

Figure 6B

Figure 6: A low (6A) and high (6B) power view of Ki-67 staining 40-50%

DISCUSSION

Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystem genetic disorder involving skin, skeletal and nervous systems. NF1 results from a mutation in or deletion of the NF1 gene located at chromosome 17q11.2; whose gene product, neurofibromin, is a tumor suppressor involved in the down-regulation of the rat sarcoma viral oncogene homologue (RAS)–mitogen activated protein kinase (MAPK) pathway. Our patient had at least 2/7 of the National Institute of Health (NIH) Consensus diagnostic criteria for NF (Image 1) (2). Lifetime risks for both benign and malignant tumors are increased in individuals with NF1.

There is an increased risk of malignant peripheral nerve sheath tumors MPNST [lifetime risk of 8-13%], paediatric rhabdomyosarcoma, paediatric neuroblastoma, juvenile hematologic malignancies, gastrointestinal stromal tumors [lifetime risk of up to 6%], somatostatinomas (duodenal carcinoids), breast cancer [lifetime risk up to 8.4% in <50yrs] and phaeochromocytomas (3). There has been no previous report of malignant phylloides tumor of the breast in NF1 in our set-up. Interstitial deletions of the short arm of Chromosome 3, del (3) (p12p14) and del (3) (p21p23) have been found in benign phylloides tumor. Whereas 3p14 is the location of the FHIT (fragile histidine triad) gene whose genetic aberrations predisposes to several malignancies, the DNA mismatch repair gene homologue hMLH1 resides in 3p21–23 and whose mutations are found in hereditary nonpolyposis colon cancer. Interestingly, the loss of the NF1 gene has been reported in a tissue sample of malignant phylloides tumor (4).

The decreased ability to repair genetic alterations increases the likelihood of mutations of oncogenes and tumor suppressor genes. Apart from the Knudson 'two-hit' model of tumorigenesis development of malignant cancers in NF1 individuals requires further acquisition of additional genetic aberrations. We propose that NF1 predisposes the patient to particularly rare malignancies. Indeed, a patient with any germline mutation (DNA mismatch repair (MMR) gene deficiency) that predisposes to a malignancy and NF1 may be susceptible with:

- An increased lifetime risk of rare malignancies
- Risk of earlier age of onset of a malignancy
- Higher rate of malignant transformation of benign tumors.

Early onset duodenal and colon cancers have been reported in children with germline homozygous MLH1mutation and NF1 contrary to middle age onset of the gastrointestinal cancers in patients with the germline homozygous mutation only. Early age development of extracolonic cancers has been seen in children with a constitutional homozygous inactivation of the hMLH1 cancer susceptibility gene and neurofibromatosis. Ricciardone et al proposed an "MMR deficiency pathway" requiring at least three steps including a heterozygous mutation creating a somatic "pro-mutator" phenotype, a wild-type allele loss producing a somatic mutator phenotype and a downstream gene mutation(s) generating a cancer phenotype that would be extremely rare due to the multiple steps required (5). The NF1 gene is a frequent somatic target in constitutional MMR deficiency (homozygous germline MMR mutations) due to its large size (59 exons spanning 350 kilobases of genomic DNA), its high mutation rate (10-fold higher than other genes at 1:10,000 alleles per generation), the high frequency of genetic recombinations with pseudogenes that act as reservoirs for mutations and the presence of repetitive sequences that are highly susceptible to mutations and intrastrand recombinations (6).

Malignant phylloides is extremely rare representing 10-15% of phylloides tumors and challenging to distinguish from the benign type (7). There are no clinical or radiological features that help distinguish a benign phylloides from a malignant phylloides. Based on the clinical behavior, our patient's breast disease likely underwent a malignant transformation. Variance between the initial FNA cytology (FNAc) which suggested benign disease and the final mastectomy histopathology which demonstrated malignant disease could indicate evolution of disease in his patient. The histopathology and immunohistochemistry of the mastectomy specimen confirmed malignant phylloides. Whereas Ki-67 of more than 25% is a poor prognostic marker in breast cancer; its role in phylloides tumors is limited to distinguishing benign from malignant phylloides. Ki-67 of 40-50% in our patient is indicative of malignant phylloides.

The patient presented with locally advanced disease negating wide local excision. We performed simple mastectomy as radical procedure would not be beneficial (8). Locally advanced malignant phylloides has a good prognosis, ten years post excision mortality is uniform when compared to the general population (9). The role of adjuvant chemotherapy, radiotherapy, hormonal therapy or biologic therapy is furthermore not clear. Despite varied oncogenic mechanisms in patients with NF1 hampering development of targeted immunologic therapy, research is still ongoing. Life Expectancy in NF1 is approximately 8 years lower than the general population (10). Impact of localized malignant phylloides on overall survival is yet to be determined. Our patient is on follow up according to NICE sarcoma guidelines and NF1 conference statement.

Challenges in management

The challenges included whether to repeat imaging of the breast and axilla as well as chest and abomino-pelvic CT scan for staging. Diagnosis proved challenging because of discrepancies between FNAc, incisional biopsy and final histopathology of mastectomy specimen. The choice and application of immunohistochemistry stains was crucial in determining appropriate diagnosis. Relevance of positive cytokeratin stains which is significant in ductal carcinoma but of unknown prognostic value in our case.

Ki67 was 40-50%, in ductal breast cancer ≥ 25% is indicative of poor prognosis but with potential good response to chemotherapy, however, application of this in malignant phylloides tumor is not known. The role of ER/PR/HER-2 status is not known and question of whether it should be evaluated is not clear. We were unable to perform molecular studies which are warranted in this case to conclusively determine presence of any germline mutation that predisposes to malignancy. Axillary dissection was a surgical dilemma in this patient in absence of evidence-based guidelines. The roles of neo-adjuvant as well as adjuvant chemotherapy and radiotherapy protocols are not established. Postoperative follow-up protocol in these patients is also not clear.

CONCLUSION

Malignant phylloides tumor of the breast in Neurofibromatosis type 1 is extremely rare and challenging especially in diagnosis and management. We recommend breast core biopsy and immunohistochemistry in NF1 patients with breast lesions; more so ensuring histopathology of excised masses following definitive surgical management. NF1 in a patient with a germline homozygous mutation of the DNA mismatch repair (MMR) gene is a predisposition to early age onset of rare malignancies.

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