NEUROFIBROMATOSIS AND NEOPLASMS-TWO INTERESTING CASES

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ABSTRACT

Neurofibromatosis is an inherited disorder with varied systemic manifestations in the soft tissues, nervous system and skin. Cutaneous manifestations include multiple neurofibromas, café-au-lait macules, Lisch nodules and intertriginous freckling. Hematopoietic neoplasms like lymphomas and leukemias have been reported. We report here two interesting neoplasms associated with neurofibromatosis. The first case is a benign chondroid syringoma of the skin, occurring as a collision tumor in synchrony with neurofibroma. The second report is of a case of chronic myeloid leukemia in an adult with neurofibromatosis. Both cases are presented here for their rarity.

KEYWORDS

Neurofibromatosis, Chondroid Syringoma, Chronic Myeloid Leukemia.

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is a common autosomal dominant inherited disorder with a prevalence of 1 in 2500 to 3300 individuals. Also known as von Recklinghausen disease type 1, the most important component of this disorder is the multiple neurofibromas. These patients are also predisposed to develop a variety of non-neoplastic manifestations and tumors including vascular lesions, lipoma, gastrointestinal stromal tumor, pheochromocytoma, Wilms' tumor and melanoma.^{1,2}

Characteristic skin lesions in NF1 include café-au-lait macules, skin-fold freckles and neurofibromas. Chondroid syringoma is a rare benign appendageal tumor of the skin of eccrine or apocrine origin. It is also called a mixed tumor of skin because of the presence of both epithelial and mesenchymal components. It has an incidence of 0.01-0.098% of all primary skin tumors.^{3,4} Synchronous occurrence of chondroid syringoma in a patient with neurofibromatosis is rare.

Patients with NF1 are at increased risk for chronic myelomonocytic leukemia, acute lymphoblastic leukemia and non-Hodgkin lymphoma. Chronic myeloid leukemia is a common hematopoietic clonal stem cell disorder characterised by proliferation of myeloid cells and the Philadelphia chromosome. Children with neurofibromatosis are 500 times more prone to myeloid neoplasms than normal children. Occurrence of chronic myeloid leukemia in association with neurofibromatosis in an adult is rare.^{5,6}

CASE REPORTS

Case 1

A 60-year-old male presented with multiple painless swellings all over his body since childhood.

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One such swelling over his forehead on the right side showed rapid growth over 4 to 5 months and was associated with pain. The forehead lesion was excised and sent for histopathology examination.

Gross

The excised specimen was a skin covered globular soft tissue mass measuring 3.3x2.2x2.0cms. Cut section showed grey-white and myxoid areas. [Figure 1].

Fig. 1: Collision tumor-neurofibroma with chondroid syringoma: gross specimen of a skin covered soft tissue mass (Left) with grey white and myxoid areas on cut surface (Right)

Microscopy

Two synchronous benign neoplasms were noted in the dermis [Figure 2]. One was a neurofibroma, composed of proliferating spindle cells with interspersed fibroblasts, capillaries and sparse mononuclear cell infiltrate [Figure 3]. Adjacent to this was a well circumscribed mixed tumor of skin with features of chondroid syringoma. The tumor comprised of tubules of varying sizes and shapes, some cystically dilated and were lined by benign bilayered epithelium [Figure 4]. The lumina of tubules showed eosinophilic material. Cholesterol clefts were noted in these secretions. The ducts were seen dispersed in a mucoid and chondroid matrix [Figure 5]. A diagnosis of collision tumor of neurofibroma with chondroid syringoma was made.

Fig. 2: Neurofibroma with chondroid syringoma-photomicrograph shows collision of two synchronous benign neoplasms (4x, H&E)

Fig. 3: Neurofibroma-photomicrograph shows proliferation of spindle cells with wavy nuclei, interspersed with fibroblasts, capillaries and sparse mononuclear cell infiltrate in a collagenous and myxoid stroma (10x, H&E)

Fig. 4: Chondroid syringoma-photomicrograph shows a tumor comprising tubules lined by benign bilayered epithelium with intervening chondromyxoid matrix (20x, H&E)

Fig. 5: Chondroid syringoma-Photomicrograph shows ducts dispersed in chondroid matrix. Also seen is a cyst filled with secretions and cholesterol clefts (4x, H&E)

Case 2

A forty-year-old male presented with history of multiple (4) soft tissue swellings of six months to one year duration. The larger one on the back measured 3x2cms and the smaller ones on the left forearm measured 1cm in diameter each. The swellings were firm, mobile and non-tender. A clinical diagnosis of neurofibromatosis was made and confirmed with fine needle aspiration cytology [Figure 6]. Patient's peripheral blood was examined as a routine workup. His hemogram was as follows: Hb-9.7gm%, total leucocyte count- more than 4.0 lakhs/cumm with immature granulocytes and platelets- 1.9 lakhs/cumm. Peripheral smear showed macrocytic RBCs, shift to left in the myeloid series with 02% myeloblasts, 03% promyelocytes, 25% myelocytes, 10% metamyelocytes, 46% bands/stabs/neutrophils, 06% eosinophils and 08% basophils [Figure 7]. A diagnosis of chronic myeloid leukemia in chronic phase was made.

Fig. 6: Neurofibroma-aspirate smear shows a tissue fragment with spindle cells trapped in collagenous stroma (20x, H&E). Inset shows comma-shaped nuclei in some cells (40x, H&E)

Fig. 7: Chronic myeloid leukemia-peripheral blood smear shows increased granulocytes with numerous myeloid precursors and neutrophils. A basophil and a normoblast are also seen in the field (100x, Leishman).

DISCUSSION

Neurofibromatosis is classified as Neurofibromatosis type 1 (NF1) and type 2 (NF 2) based on the genes involved. NF1 is also known as von Recklinghausen's disease and is the most common form.^{7,8} It is a common autosomal dominant neurocutaneous disorder with a predisposition to develop benign and malignant tumors. Patients with NF1 are at two to five times increased risk for developing neoplasms compared to normal population. These include CNS, hematopoietic and skin neoplasms.^{7,9}

The disease is caused by loss of function mutations in NF1 gene, a tumor suppressor on chromosome 17q11.2, that encodes neurofibromin. Neurofibromin is a guanine triphosphatase-activating protein and a negative regulator of RAS proto-oncogene. This protein contains a functional GAP domain that acts on RAS-GTP, thereby playing a role in regulating RAS function. Loss of neurofibromin leads to excess RAS activity and uncontrolled cell proliferation and tumorigenesis.¹ RAS activation induces cell proliferation in response to extracellular stimuli. Increased levels of RAS- GTP are found in NF1-associated leukemias and such leukemic cells show hypersensitivity to GM-CSF and other cytokines.^{10,11}

Dermatologic manifestations of neurofibromatosis are characterized by café-au-lait macules, Lisch nodules, intertriginous freckling and malignant neoplasms including malignant melanoma, basal cell carcinoma and Merkel cell carcinoma.^{7,8} Chondroid syringoma is a benign mixed tumor of the skin with epithelial and mesenchymal components. It presents as subcutaneous mass, typically located in the head and neck region.² A collision tumor is described as association of two different neoplasms in the same patient.¹² Neurofibromatosis colluding with chondroid syringoma is a rare occurrence.

Hematopoietic malignancies known to be associated with neurofibromatosis include lymphomas, chronic lymphoid leukemias, juvenile chronic myelomonocytic leukemia and myelodysplastic syndrome.¹⁰ Children with neurofibromatosis have 500 times greater risk of developing a malignant myeloid disorder than the normal children.

However, this association has rarely been demonstrated in adults.¹³ Very few cases of chronic myeloid leukemia have been reported to co-exist with neurofibromatosis.¹⁰

Chronic myeloid leukemia is a pluripotential stem cell disorder characterised by anemia, markedly elevated leucocyte count with shift to left in the myeloid series, basophilia, often thrombocytosis and splenomegaly. The hematopoietic cells contain a reciprocal translocation between chromosomes 9 and 22 in more than 95% of patients, referred to as the Philadelphia (Ph) chromosome [t (9; 22) (q34; q11), abbreviated as t(Ph)]. The fusion product expressed by the BCR-ABL gene leads to malignant transformation because of the abnormally regulated enzymatic activity of the chimeric tyrosine protein kinase.¹⁴

Olayemi et al.⁵ in their report on an adult with neurofibromatosis type 1 who developed chronic myeloid leukemia suggest a possible synergistic action between the absence of neurofibromin and the presence of tyrosine kinase activity of BCR/ABL gene.

CONCLUSION

Neurofibromatosis is a genetically distinct and common disorder with a known association with neoplasms and non-neoplastic pathology. However, its association with chondroid syringoma and chronic myeloid leukemia is rare. This coexistence could be incidental or resulting from a genetic defect associated with neurofibromatosis. Clinicians managing patients with neurofibromatosis should be aware of these associations.

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