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CASE-BASED REVIEW
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Neurofibromatosis Type I and Hodgkin Lymphoma: Case Report and Review of the Literature

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What is already known on this topic?

Neurofibromatosis 1 (NF1) is a tumor susceptibility syndrome. The most common malignancies associated with NF1 are gliomas, malignant peripheral nerve sheath tumor, pheochromocytomas, rhabdomyosarcoma, gastrointestinal stromal tumors, breast cancers, melanomas, and hematologic malignancies such as leukemias and non-Hodgkin lymphomas (HLs).
However, HL is very rare in individuals with NF 1.

What this study adds on this topic?

We present a patient with neurofibromatosis 1 (NF1) who further developed Hodgkin lymphoma (HL). We also reviewed the literature and brought together all the reported cases. Thus, it is aimed to keep in mind that HL may develop in the follow-up of individuals with NF.

ABSTRACT

Objective: Neurofibromatosis 1 is an autosomal dominant inherited tumor susceptibility syndrome. Individuals with neurofibromatosis 1 have a 4-5 times increased risk of malignancy compared to the general population. Central nervous system and soft tissue tumors are common non-hematological malignancies in individuals with neurofibromatosis 1. Although the association of leukemia and non-Hodgkin lymphoma as hematologic malignancies in neurofibromatosis 1 has been reported frequently in the literature in these individuals, association with Hodgkin lymphoma has been reported very rarely.

Materials and Methods: We presented a patient with neurofibromatosis 1 who further developed Hodgkin lymphoma and reviewed the literature.

Conclusion: Although rare, Hodgkin lymphoma can develop in individuals with neurofibromatosis 1. Hodgkin lymphoma should be kept in mind in cervical/supraclavicular lymphadenomegalies when evaluating patients with neurofibromatosis 1.

Keywords: Neurofibromatosis, Hodgkin lymphoma, cancer predisposition, pediatrics

Neurofibromatosis 1 (NF) is a tumor susceptibility syndrome with an autosomal dominant inheritance with an incidence of 1 : 2500-1 : 3000 individuals worldwide.[1] The mutation responsible for the development of the syndrome occurs in the NF1 gene located on the 17th chromosome. The NF1 gene encodes the neurofibromin tumor suppressor protein that functions as a Ras-GTPase activating protein. Mutations in NF 1 gene cause overactivation of the RAS/Raf/ERK signaling pathway, which is related to the development of the neoplasms in neurofibromatosis type 1.[2] The risk of developing cancer in individuals with NF1 is increased 4-5 times compared to the general population.[3] In the literature, the most common nonhematologic malignancies associated with NF1 are gliomas, malignant peripheral nerve sheath tumor (MPNST), pheochromocytomas, rhabdomyosarcoma, gastrointestinal stromal tumors (GIST), breast cancers, melanomas, and hematologic malignancies such as leukemias and non-Hodgkin lymphomas (HLs).[4] The association of HL with NF1 is very rare and only 10 cases, including ours, have been reported in the English literature.[5-11] We present a young adult patient with NF1, who was treated for optic glioma as a child, who further developed HL as an adolescent and we review the literature.

A 6-year-old girl presented to the pediatrics clinic with decreased visual acuity. She was reported to have multiple café-au-lait spots on the trunk since the age of 18 months. On the MRI, fusiform thickening consistent with optic glioma involving the prechiasmatic component of the left optic nerve and the entire right optic nerve was observed. Hamartomas in bilateral cerebellar hemispheres, brachium pontis, and left pontomesencephalic neural parenchyma were also detected. She was diagnosed with optic glioma.

Chemotherapy, consisting of vincristine and carboplatin, was started due to the progression of the right chiasmatic lesion compared to previous imaging studies and deterioration

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in visual acuity. During treatment, regression of the thickening of the optic nerve and improvement in visual acuity was achieved. Treatment was stopped after 1 year of chemotherapy. She presented with a swelling on the left forearm when she was 14 years old. MRI was consistent with a neurofibroma, in the multidisciplinary tumor board, it was decided to follow-up with the orthopedic surgeons. It has been stable since then. At the age of 18 years, she presented with lymphadenopathies in the cervical and supraclavicular region. Ultrasonographic investigation showed lymph nodes, the largest of which was 3 cm in diameter with increased vascularity. A positron emission tomography-computed tomography scan revealed an intensely 18F-fluorodeoxyglucose-avid bilateral cervical, supraclavicular, mediastinal, and abdominal lymph nodes and a lesion in the spleen. An excisional biopsy of the cervical lymph node revealed HL classic type, mixed cellularity subtype. Immunostaining was positive for CD30, Pax-5, EBV-LMP, and fascin and negative for CD15. She was diagnosed as HL-stage IIIsA. She was treated with 4 courses of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) according to our institutional protocol.[12] After 2 courses of ABVD, a full metabolic and anatomic response was attained. After 4 courses the patient was discussed in the tumor board, due to the risk of radiotherapy-induced secondary malignancies in NF1, no radiotherapy was used. The patient is under regular follow-up with no evidence of disease for 28 months. This was the only case with NF1 and HL in our cohort of 237 HL cases (0.4%), and the only case with HL in our cohort of 81 (1.2%) NF1 and malignancy cases diagnosed over 27 years.

Neurofibromatosis is a neurocutaneous disorder and tumor predisposition syndrome that occurs as a result of autosomal dominant mutations in the NF1 gene on chromosome 17 and is characterized by hyperpigmented macules (café-au-lait macules), axillary and/or goin freckling and benign tumors of the nerve sheath (neurofibromas), Lisch nodules, bony dysplasias, and optic pathway gliomas.[1,2,13] With mutations in the NF1 gene, the loss of function occurs in neurofibromin, which keeps the protooncogene Ras in inactivated diphosphorylated form causing an increase in Ras activity, especially in neurocutaneous tissues, leading to tumorigenesis. Apart from the germline mutations in NF1, somatic mutations of NF1 are also known to cause the development of various sporadic malignancies such as lung cancer, colon cancer, ovarian cancer, breast cancer, and leukemia.[14] The overall risk of cancer for individuals with NF1 is found to be 2.7-4 times higher than in the general population.[15,16] The most common neoplasms observed in patients with NF1other than neurofibromas include low-grade gliomas, MPNST, breast cancer, high-grade gliomas, pheochromocytoma, GIST, and melanoma.[17] Among hematological malignancies, leukemias, and non-HL are found to be associated with NF1.[18,19] Hodgkin lymphoma accompanying NF1 is extremely rare and there are only 10 cases of HL accompanying NF1 including ours in the English literature (Table 1).[5-11] In a retrospective review of the records of 16 564 childhood cancer cases, Narod et al[5] reported that 90 of these patients had NF and 2 had developed HL.

Compared to other lymphoma types, relatively little is known about the genetic background of HL. The malignant Hodgkin- and Reed- Sternberg (HRS) cells constitute a very small part of the tumor tissue, typically less than 1%.[20] The relatively small number of HRS cells increases the feasibility of genetic testing in non-malignant tissue. Therefore, many genetic techniques fall short of revealing the underlying genomic defect. Thanks to advances in genomic technologies, the genetic cornerstones of HL are much better understood. Among these, the best-known genetic changes are mainly in TNF receptor–associated factors (TRAFs) Nuclear factor-κB (NF-κB) Janus kinase-signal transducer and activator of transcription (JakSTAT) pathways.[21-23] Until now, no relationship between HL and changes in NF1 genetics has been demonstrated in the literature.

In this paper, we reported a case of an 18-year-old girl with NF1 and a history of treatment for optic glioma who has developed HL. NF-1 cases should be under regular follow-up due to the increased risk of malignancies. In NF-1 cases, neurofibromas, malignant peripheral nerve sheath tumors, sarcomas come to mind primarily when palpable lesions develop because they are more common in NF1. We want to emphasize that HL should be kept in mind in cervical/supraclavicular lymphadenomegalies when evaluating patients with NF1.

Table 1. Cases of Hodgkin Lymphoma in Patients with Neurofibromatosis Found in the Literature

References	Age at Diagnosis of HL (years)	Sex	NF type	Hodgkin Subtype	Cancer stage at diagnosis	Treatment	Outcome	Status at Last Follow-up
Narod et al[5]	NA	NA	NF	NS	NA	NA	NA	NA
	NA	NA	NA	NS	NA	NA	NA	NA
Natori et al[6]	70	Male	NF1	NA	NA	MOPP+RT (5 courses)	CR	Died of other cause
Dang and Cohen[7]	32	Male	NF 1	NA	Stage I	NA	NA	In remission
Vázquez-Osorio et al[8]	5	Male	NF1	NA	NA	NA	NA	NA
İncecik et al[9]	8	Male	NF1	NA	NA	NA	NA	NA
Bergqvist C[10]	30	Female	NF1	NA	NA	NA	NA	In remission
	NA	Female	NF1	NA	NA	NA	NA	
Cabrera et al[11]	16	Female	NF1	NS	Stage IIA	ABVD (4 courses)	CR	In remission
Our case	18	Female	NF1	MS	Stage IIIsA	ABVD (4 courses)	CR	In remission

NA, not available; HL, Hodgkin lymphoma; NF, neurofibromatosis; CR, complete remission; MOPP, nitrogen mustard, vincristine, procarbazine, prednisone; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; NS, nodular sclerosing; MS, mix cellularity; RT, radiotherapy.

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