ELSEVIER

Critical Reviews in Oncology/Hematology 86 (2013) 191–199

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Neurofibromatosis type 1, gastrointestinal stromal tumor, leiomyosarcoma and osteosarcoma: Four cases of rare tumors and a review of the literature

Çiğdem Usul Afşar[a,*], İsmail Oğuz Kara[a], Banu Kara Kozat[b], Haluk Demiryürek[c], Berna Bozkurt Duman[a], Figen Doran[d]

[a] *Cukurova University Medical Faculty, Department of Medical Oncology, Adana, Turkey*
[b] *Adana Numune Education and Research Hospital, Department of Gastroenterology, Adana, Turkey*
[c] *Cukurova University Medical Faculty, Department of General Surgery, Adana, Turkey*
[d] *Cukurova University Medical Faculty, Department of Pathology, Adana, Turkey*

Accepted 8 November 2012

Contents

Abstract

Background: Neurofibromatosis type 1 (NF1) is a genetic syndrome that predisposes patients to benign and malignant tumor development. Patients with NF1 develop multiple neurofibromas that can transform into aggressive sarcomas known as malignant peripheral nerve sheath tumors. In contrast, malignant tumors unrelated to the nervous system rarely coexist with neurofibromatosis. The aim of this article was to present four cases of adult NF1 patients with malignant tumors unrelated to the nervous system as well as a bibliographic search for papers describing these tumors in NF1, focusing on osteosarcomas, gastrointestinal stromal tumors (GISTs), leiomyosarcomas and somatostatinomas and their genetic alterations in NF1.

Methods: Search engines such as PubMed and MEDLINE were browsed for English-language articles since 1989 using a list of keywords, as well as references from review articles. Search terms were NF1, osteosarcoma, leiomyosarcoma, somatostatinoma and GIST. Data were summarized in a table at the end of the Results section.

Results: In our four NF1 cases, there were one osteosarcoma, one leiomyosarcoma, one somatostatinoma and GIST and one GIST. NF1 was diagnosed at an adult age when these patients were admitted to our oncology department. The results generated by the literature search yielded 75 articles about NF and GIST. We summarized the clinical characteristics of 43 patients with NF1 and somatostatinoma. Forty-five articles involving NF and osteosarcoma were found, and of these, 26 involved NF1; from these articles, we identified the clinical features of 8 patients. Twenty-five articles were found concerning NF1 and leiomyosarcoma, and of those, we summarized the clinical features of 15 patients.

* Corresponding author. Tel.: +90 3223386060x3143.
E-mail address: cigdemusul@yahoo.com (Ç.U. Afşar).

http://dx.doi.org/10.1016/j.critrevonc.2012.11.001

Conclusions: Here we reviewed somatostatinomas, GISTs, osteosarcomas and leiomyosarcomas occurring in NF1 patients. Patients with NF1 who present with gastrointestinal symptoms, should be carefully evaluated carefully with a high index of suspicion of potential GISTs, periampullary and duodenal tumors. Patients with pathological fractures or bone pain along with NF1 should be carefully screened for malignant bone tumors. Patients with NF1 can develop leiomyosarcoma less frequently than other malignancies, but the association of uterine leiomyoma and NF1 may not be fortuitous. Somatic mutations were defined for frequent tumors, including neurogenic tumors and GISTs but not for sarcomas due to the complexity of underlying mechanisms of the disease and tumorigenesis. Based on the findings; all NF patients can develop malignant tumors, including the less frequently observed ones. Therefore, we recommend that new genetic studies should be performed for rare malignancies in cases of NF1.

Keywords: Neurofibromatosis type 1; GIST; Somatostatinoma; Osteosarcoma; Leiomyosarcoma

1. Introduction

NF1, or von Recklinghausen disease, is an autosomal dominant genetic disorder caused by mutations in the neurofibromin 1 gene, which encodes the tumor suppressor neurofibromin [1,2]. NF1 is the most frequent subtype of neurofibromatosis (approximately 97% of NF patients), with an incidence of approximately 1 in 3500 live births [3].

NF1 is characterized by multiple café au lait spots, axillary and inguinal freckling, multiple discrete dermal neurofibromas, and iris hamartomas known as Lisch nodules. Less commonly observed (but potentially more serious) manifestations of the disease include plexiform neurofibromas, optic and other central nervous system gliomas, malignant peripheral nerve sheath tumors (MPNST), vasculopathy, and osseous lesions. Bone dysplasia results in scoliosis [4,5]. Neurological symptoms observed in NF1 include epilepsy, intellectual disability and difficulty learning. The diagnostic criteria for NF1 were defined by the NIH Consensus Development Conference in 1988 (Table 1).

The pathological manifestations of NF1 are extremely variable, even within a family. Mutations result in a predisposition to developing a variety of tumors of the central and peripheral nervous systems, as well as other malignancies. However, the occurrence of malignant tumors unrelated to the nervous system is rare [6]. GISTs, somatostatinomas, periampullary tumors, breast cancer, pheochromocytomas, and less frequently, soft tissue sarcomas (STS) and leukemia–myelodysplasia syndrome, are all observed in adults with NF1 [7–9]. NF1 patients have a high risk of developing STS, and particularly malignant peripheral nerve sheath tumors, often with aggressive clinical presentation and poor outcome [10]. In the literature, there is one report of a patient with NF1 who simultaneously, had polymyositis, asymptomatic pheochromocytoma, and primary hepatic leiomyosarcoma [11].

NF1-associated GISTs are not very rare, but account for less than 5% of all GISTs reported. NF1 patients are at higher risk for developing GISTs than the general population [12]. GISTs in NF1 patients have a high prevalence in the small intestine [13,14].

Table 1
Diagnostic criteria for NF1 as defined by the NIH Consensus Development Conference in 1988 [49].

-6 or more café-au-lait spots (>0.5 cm in children or >1.5 cm in adults)
-2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
-Axillary or groin freckling
-Optic pathway glioma
-2 or more Lisch nodules (iris hamartomas observed on slit lamp examination)
-Bony dysplasia (sphenoid wing dysplasia, bowing of long bone, pseudarthrosis)
-First degree relative with NF1

2. Methods

Publications were identified by browsing search engines such as PubMed and MEDLINE for English-language articles since 1989 using a list of keywords; as well as identifying references from review articles. The following keywords were used for searching databases: NF1, osteosarcoma, leiomyosarcoma and GIST. Data were summarized as a table at the end of results. We evaluated four cases of NF1 with rare malignancies by searching patients' folders, and treatment strategies were discussed. Possible genetic alterations in these tumors were evaluated. Two of the cases evaluated had GİSTs, one had osteosarcoma and one had leiomyosarcoma. Pathology reports of these patients were assessed at the same hospital; Cukurova University of Medicine, Adana, Turkey.

3. Clinical material

3.1. Patient 1

In our first patient; we report an unusual case of osteosarcoma, a high-grade malignant bone tumor, arising in the femur of an NF1 patient. The patient was a 17-year-old man who had café-au-lait spots and neurofibromatosis of the skin over his whole body, with von Recklinghausen disease (NF1) diagnosed by the authors. One of his brothers was also diagnosed with NF1 in our clinic. There was a consanguineous marriage between his parents. At the age of 16, he underwent marginal excision of a 2×1 cm soft tissue mass in the left neck region. Histological findings from