Thyroid fibrosarcoma associated with neurofibromatosis type 1: A case report

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ABSTRACT:

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Neurofibromatosis (NF) is a neurocutaneous genetic disorder that is associated with various clinical phenotypes expressed by neural crest-derived organs including nervous, cutaneous and skeletal systems[1]. Among various types, NF type 1 (NF-1) has the most specific skin features and diagnostic criteria. It is inherited as an autosomal dominant fashion with an incidence of 1 in 3,000 live births; however, approximately 50% of cases are due to spontaneous mutation[2]. Besides, there are well-established associations of benign and malignant tumors with NF-1, most of which are of neural origin such as optic pathway tumors[3], and particularly malignant peripheral nerve sheath tumors[4]. On the contrary, few cases are reporting the co-existence of non-neurogenic sarcomas with NF-1[5].

In this report, we present a patient with rare non-neurogenic sarcoma, thyroid fibrosarcoma, uncommonly associated with NF-1.

Key words: Neurofibromatosis type 1, thyroid fibrosarcoma

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Case report

A 34-year-old Thai woman presented with a progressively expanding, non-painful mass, approximately 10 cm in diameter, on the right side of her neck for three years (no images available at the time of presentation). Neither dysphagia, hoarseness of voice nor constitutional symptoms were observed. In addition, she also had brownish macules and patches distributed on her torso since she was young. Skin examination showed generalized freckling, multiple café-au-lait macules (CALMs) and patches, variable in sizes from 15 mm to 45 cm in diameter on her torso, and a few non-tender dermal nodules on the extremities. Eye examination showed multiple Lisch nodules on both irises (Fig. 1). Other physical examinations were within normal limits. Of note, her father died due to an unknown skin cancer at the age of 50.

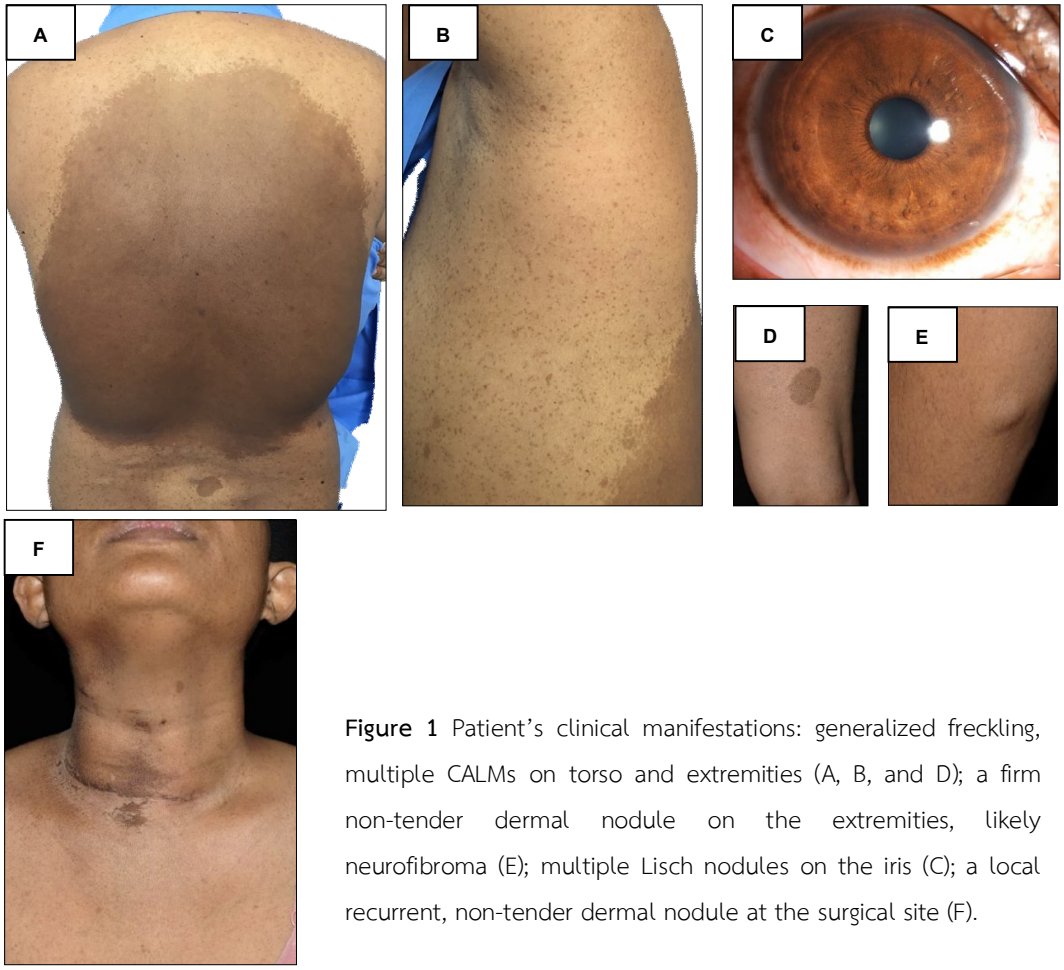

Figure 1 Patient's clinical manifestations: generalized freckling, multiple CALMs on torso and extremities (A, B, and D); a firm non-tender dermal nodule on the extremities, likely neurofibroma (E); multiple Lisch nodules on the iris (C); a local recurrent, non-tender dermal nodule at the surgical site (F).

According to her skin findings, the diagnosis was compatible with NF-1. Initially, right thyroid lobectomy with isthmectomy was performed with a pathological report suggesting medullary thyroid carcinoma. After her first operation, the computed tomography (CT) scan of the larynx, infrahyoid, neck and abdomen revealed an enlarged mixed solid-cystic mass occupying the right carotid sheath with pressure effect and hepatic metastasis. Therefore, total thyroidectomy with right modified radical neck dissection was performed, and the final pathology report was fibrosarcoma grade 3, confirmed by immunohistochemical staining (Fig. 2).

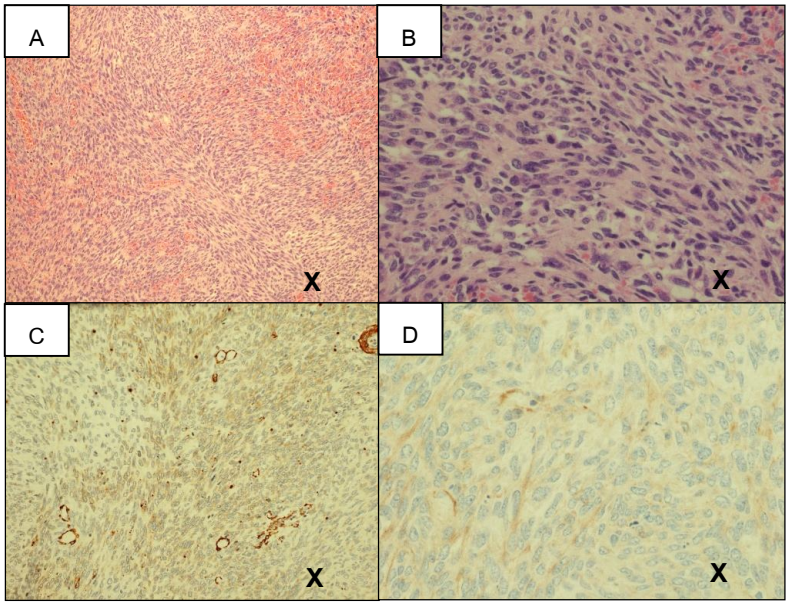

Figure 2 Histopathological findings showed the neoplastic cells were arranged in fascicular pattern with focus patternless by H&E (A; H&E, X200). The cells posed plump spindle-shaped, moderate pleomorphic nuclei, coarse chromatin and indistinct nucleoli (B; H&E, X400). SMA staining (C; X200) and MSA staining (D; X400) were focally positive. Furthermore, AE1/AE3, TTF1, S100 and calcitonin were negative. Mitosis count > 19 mitoses/10 high-power fields, necrosis < 50%. The diagnosis was compatible with fibrosarcoma, grade 3 (FNCLCC grading system).

After her second surgery, she developed hypocalcemia and right true vocal cord paresis, the former for which was treated with calcium carbonate 3,000 mg/day, calcitriol 0.5 mcg/day and levothyroxine 100 mcg/day. Further, she continued concurrent palliative radiotherapy and chemotherapy.

Two months post-surgery, her physical examination showed a local recurrent soft, non-tender dermal nodule, approximately 2.5 cm in diameter, at the previous surgical site on the right and anterior side of her neck (Fig. 1F). The CT scan revealed a local recurrence tumor at the right thyroid bed with pressure effect on adjacent structures and multiple lung metastases.

Discussion

The mutation of the *NF1* gene, known as a tumor suppressor gene encoding neurofibromin, is the primary pathogenesis of NF-1. Neurofibromin can be found in a variety of cell types, especially in the neurons or Schwann cells. Its major role is to control cell proliferation by downregulating the downstream effects of the RAS pathway. Thus, low level of intracellular neurofibromin hyperactivates RAS pathway which results in various clinical manifestations of NF-1, including abnormal skin pigmentation and tumorigenesis[2]. NF-1 belongs in the RASopathies, a group of entities with abnormalities in the RAS pathway[6].

There are multiple types of tumors related to NF-1. Most of them are derived from neural crest in origin. The examples include optic glioma, benign neurofibroma, and plexiform neurofibroma in which the latter carries the risk of malignant transformation into malignant peripheral nerve sheath tumor (MPNST). However, non-neurogenic benign and other malignant tumors were also reported, such as pheochromocytoma, gastrointestinal stromal tumors, juvenile xanthogranuloma, and rhabdomyosarcoma[2,5]. In addition, the pathogenesis of malignant transformation in these tumors was hypothesized to result from second-hit mutation of *NF1* gene cooperating with other additional gene mutations, for example, the *TP53* mutation found in MPNST[2].

Interestingly, no reports in the past ten years showed the association between NF-1 and thyroid fibrosarcoma as in our patient. Although this type of tumor is scarce, it behaves aggressively with multiple local recurrences. The 2-year survival rate is less than 70%[7]. Due to vague clinical signs and symptoms, the histopathological study is the most appropriate tool for diagnosis. Microscopically, it is composed of hypercellular spindle cell tumors arranged in fascicular or typical herringbone pattern[8]. The exact pathomechanistic relations between thyroid fibrosarcoma and NF-1 have not been elucidated. However, resembling other

soft tissue sarcomas concurrent with NF-1[5], we speculate that the second-hit mutation with hyperactivation of the RAS pathway might be involved. Further investigations may be essential to clarify these associations.

Because of its rarity, the treatment of fibrosarcoma is not well-demonstrated. However, a local wide excision with adjuvant radiotherapy is usually recommended[8]. In our patient, palliative radiation followed by chemotherapy was chosen due to the advanced stage of her disease.

In conclusion, we report a case of NF-1 associated with an uncommon tumor, thyroid fibrosarcoma. Awareness and life-long surveillance for malignancy development and transformation should be highly recommended in patients with NF-1.

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