Typical presentation of neurofibromatosis type I in a patient with giant cutaneous neoplasm and café au lait spots: A case report

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Received January 17, 2024; Accepted May 28, 2024

DOI: 10.3892/br.2024.1905

Abstract. Neurofibromatosis type 1 (NF1), which is also known as von Recklinghausen's disease, is a multisystem genetic disease that is principally associated with cutaneous, neurologic and orthopedic manifestations. The present case report described an unusual case with a giant cutaneous neoplasm on the right breast skin of a 36-year-old female who was admitted to the Department of Breast Surgery at the Affiliated Tumor Hospital of Xinjiang Medical University (Urumqi, China). Skin mass excision was performed and histopathology confirmed the diagnosis of thoracic plexiform neurofibroma as a primary presentation of NF1. The clinical implementation of NF1 therapies necessitates meticulous consideration of various factors and should involve a multidisciplinary team with expertise in NF1.

Introduction

Neurofibromatosis (NF) is a genetic disorder manifested by tumor formation in the central or peripheral nervous system. It comprises three types and NF type 1 (NF1; Online Mendelian Inheritance in Man no. 613113) is an autosomal dominant genetic disorder exhibiting a range of manifestations such as café-au-lait spots, skinfold freckling, cutaneous neurofibromas and Lisch nodules in the iris, also known as von Recklinghausen's disease (1). Von Recklinghausen, in 1882, was the first to recognize that the tumor arises from nervous tissue. The prevalence of NF1 is estimated to be ~1 in 3,000 individuals worldwide, making it one of the most common genetic disorders (2). The NF1 gene, which codes for neurofibromin, is positioned on chromosome 17 at the locus 17q11.2 (3). Neurofibromin, a tumor suppressor protein, is synthesized in neurons, oligodendrocytes and Schwann cells, where it acts as a Ras-GTPase activating protein. NF1 has almost 100% penetrance but variable expression and 50% of cases are sporadic (4). NF1 is typically diagnosed based on clinical criteria established by the National Institutes of Health (NIH). The diagnosis frequently involves the presence of specific clinical features such as café-au-lait spots, neurofibromas, freckling, Lisch nodules and a family history of NF1. Genetic testing can also be used to confirm the diagnosis by identifying pathogenic mutations in the NF1 gene. More than half of patients with NF1 also have plexiform neurofibroma (PN). Individuals with NF1 have a significantly increased risk of malignancy and a reduced life expectancy compared to the general population (5). Early and accurate diagnosis of NF1 is crucial for appropriate management and monitoring of the disorder and its potential complications.

The present study reported on the case of a 36-year-old female patient with a sizable mass on the right chest wall. The mass's base was located above the right breast, extending to the patient's thigh when standing. The patient, facing mental stress and financial challenges, had not sought any medical care. Eventually, the patient presented at our department due to the substantial impact of the mass on her daily life.

Case report

In July 2022, a 36-year-old female with giant cutaneous neoplasm on the right breast skin presented at the surgical outpatient department of the Affiliated Tumor Hospital of Xinjiang Medical University (Urumqi, China), requesting the excision of a large neurofibroma. Upon examination, a large tumor was observed extending downward from the skin on the right side above the breast and there were numerous soft, fleshy and non-tender nodules of varying sizes, along with brown-pigmented macules mainly distributed on the chest, waist and upper arms. The patient could only report that she had had them for as long as she could remember and the neoplasm on the right breast skin had enlarged markedly after her giving birth to her four children. The clinical features corresponded to a diagnosis of NF1. The patient has a family history of related diseases, as the patient's father has extensive

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Key words: neurofibromatosis type 1, café au lait spots, diagnosis, treatment

cutaneous nodules and the patient's children are also affected. Preoperative photographs are provided in Figs. 1-4.

Auxiliary examinations were as follows: Ultrasonic imaging revealed a large neoplasm on the skin above the right breast with an indeterminate size and unclear demarcation between the base and the skin. Thoracic CT scan indicated skin thickening of the right anterior chest wall and thus, skin malignancy was considered; multiple nodules were present in the right thoracic muscular space, and thus, metastases were suspected; sternum destruction and an abnormal shape and position of the sternum, with forward protrusion, suggested a congenital developmental abnormality; multiple nodules were observed on the skin surface and subcutaneous tissue of the chest and back, and metastases were suspected. Typical ultrasound images and CT scans are shown in Fig. 5.

Surgical excision is the mainstay of treatment for cutaneous neurofibromas, but local recurrence is possible (6). After completion of the auxiliary examinations, the patient underwent a neurofibro-resection and the skin of the chest was sutured using the oncoplastic technique in July 2022, one week after her first presentation at surgical outpatient department. An incision was made at the base of the skin appendage on the right chest wall, extending through the skin and subcutaneous tissue to the pectoralis muscle. Hemostasis was meticulously maintained during the procedure, followed by excision of the excess appendage for rapid pathological evaluation. The rapid pathological results, produced according to standard protocols, indicated a mesenchymal tumor with diffuse spindle cell proliferation, displaying a mild morphology, partial stromal edema and localized deposition of pigment granules, suggesting a probable benign or borderline nature. The surgery lasted 120 min, with two disposable drainage tubes placed intraoperatively - one in the chest wall and the other in the right axilla. On the first postoperative day, 150 ml of drainage from the axilla tube and 40 ml from the chest wall tube were recorded. At three days after the surgery, the drainage from both of the patient's tubes decreased to <10 ml, with the drainage fluid exhibiting a pale red color. Subsequently, all drainage tubes were removed before the patient's discharge. A tumor measuring 33x25x3.5 cm had been excised. Postoperative photographs are provided in Figs. 6 and 7. Subsequent histopathological examination, performed according to standard protocols, of the massive tumor on the right chest wall indicated the following: Spindle cell tumor with focal myxoid change, consistent with neurofibroma based on immunohistochemical staining and tissue morphology; tumor tissue visible at the surgical margin and base. Another smaller neurofibroma was excised during the surgery with the dimensions of 3.0x2.5x1.5 cm. The immunohistochemistry results were as follows: S-100 (+), SOX10 (+), CD34 (+), Ki-67 (+, <1%), smooth muscle actin (SMA) (-), and Desmin (-) (7). The antibodies used according to standard protocols were as follows: S-100 (cat. no. ab183979; 1:1,000 dilution; Abcam), SOX10 (cat. no. ab227680; 1:100 dilution; Abcam), CD34 (cat. no. ab81289; 1:2,500 dilution; Abcam), Ki-67 (cat. no. ab16667; 1:200 dilution; Abcam), SMA (cat. no. ab5694; 1:100 dilution; Abcam) and Desmin (cat. no. ab32362; 1:2,000 dilution; Abcam) The histopathological results of the cutaneous nodules were consistent with neurofibroma. Images from the pathological examination are provided in Fig. 8.

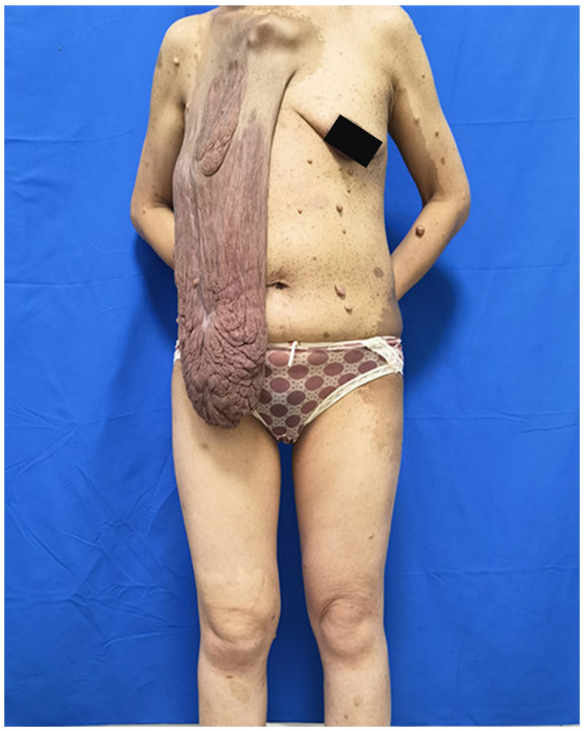

Figure 1. Preoperative anterior view showing a giant mass downwards from the right skin above the breast measuring 66x33 cm, covering the right breast.

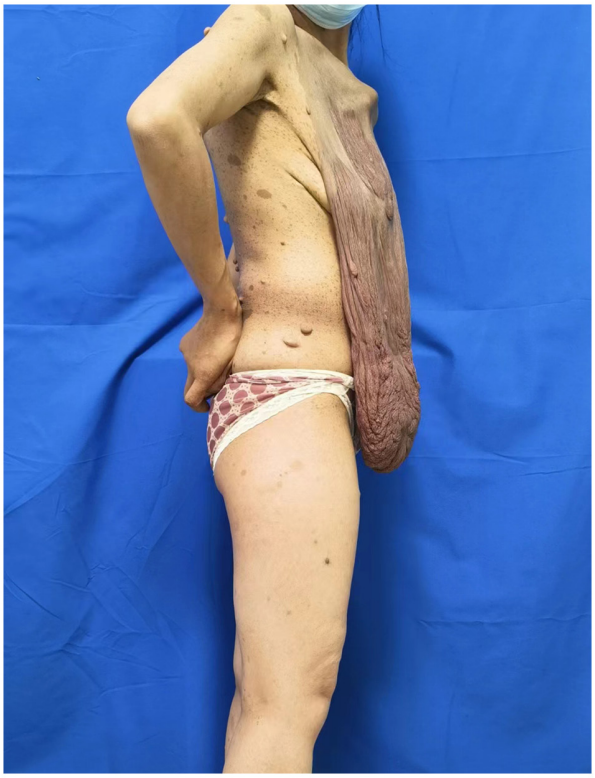

Figure 2. Right lateral view showing the outline of the breast beneath the giant skin neoplasm on the right chest.

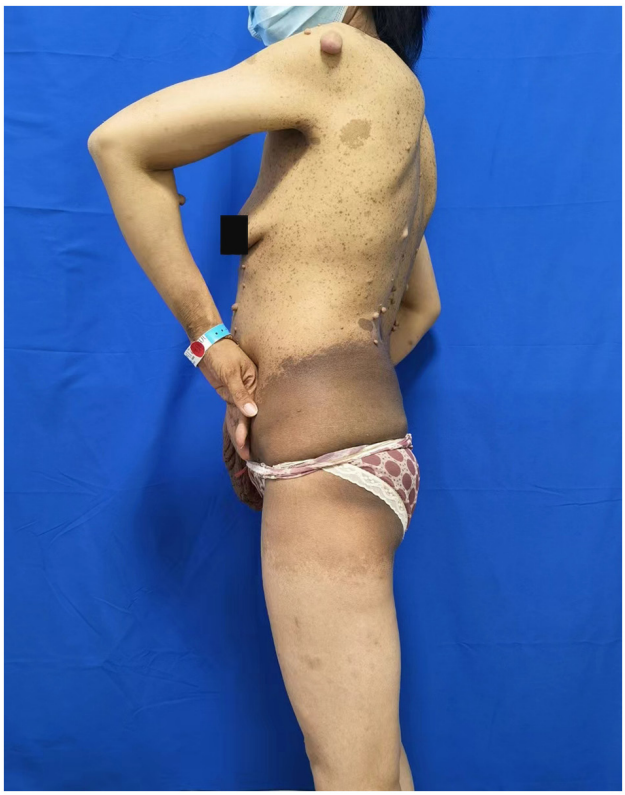

Figure 3. Left lateral view showing a skin mass measuring 3x2 cm on the upper arm and café-au-lait spots (40x30 cm^2) prevailed on the left waist and buttock.

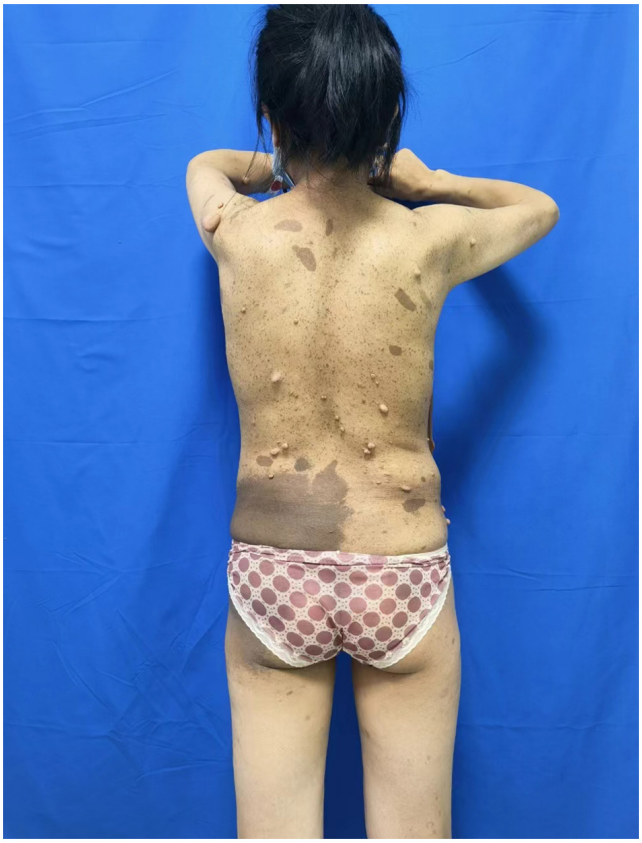

Figure 4. Preoperative posterior view showing numerous skin neoplasms and extensive café-au-lait spots on the back. The largest one is located on the left waist and buttock region.

The patient remained hospitalized for 6 days postoperatively and was then discharged in August 2022, one week after the operation. Due to the extensive scope of the lesion, complete excision was not feasible. The patient and family were informed of the situation before the surgery and consent was obtained after full explanation to them. At one month after discharge, the patient was followed up at the surgical outpatient department of our hospital in September 2022. The patient made a good recovery and the patient's life quality significantly improved.

Discussion

There is currently no treatment available for the underlying genetic defect that causes NF1. The treatment of patients with NF1 is based on identifying manifestations of NF1 and treating the complications induced by them (8). Approximately 30% of individuals with NF1 exhibit symptoms associated with PN. PN are a common manifestation of NF1, representing a histologically benign neurofibroma (9). In the current study, the case of a 36-year-old female patient with a PN on the right anterior chest since birth, gradually increasing in size, was presented. Due to financial hardship and psychological stress, the patient delayed regular check-ups until the tumor significantly impacted her daily life. Preoperatively, the patient underwent head and chest CT scans, revealing sternal protrusion, suggesting a congenital anomaly. Factors affecting PN symptoms and complications include tumor location, size, nerve involvement and age. Typically, younger patients experience faster tumor growth, while older adolescents and adults often have slower progression (10). Symptoms vary based on PN location, including impairments in vision or hearing, airway obstruction, speech and swallowing difficulties, motor dysfunction, gastrointestinal or bladder issues, deformities, as well as common symptoms such as pain and reduced mobility (11).

Psychological aspects should not be overlooked in addition to physical symptoms. Reports indicate that approximately one-third of children and adolescents with PN may display anxiety, depression and social withdrawal, impacting mental health and quality of life (12). The patient stated that the sizable mass caused significant mental distress, impacting her social life and having deterred her from seeking professional assistance for an extended period. PN have the potential to evolve into atypical neurofibromas (AN). Rapid PN growth in adults may suggest malignancy, with pain being a prominent feature in patients with AN, necessitating comprehensive evaluation for progressive severe pain in patients with PN (10). All patients with NF1 should undergo imaging studies, such as MRI and CT, to identify and monitor PN growth (13). In the case reported in the present study, the patient did not undergo MRI due to financial constraints. A biopsy for histological PN diagnosis is typically unnecessary unless malignancy is suspected based on clinical or imaging findings (14). In this instance, the patient exhibited no pain symptoms, with slow tumor growth, and was postoperatively diagnosed with a spindle cell tumor. The extensive size of the patient's tumor posed challenges for curative surgery, given its invasion of the surrounding normal tissues. The family was briefed on the pertinent surgical details prior to the operation and they provided written consent for the surgical intervention.

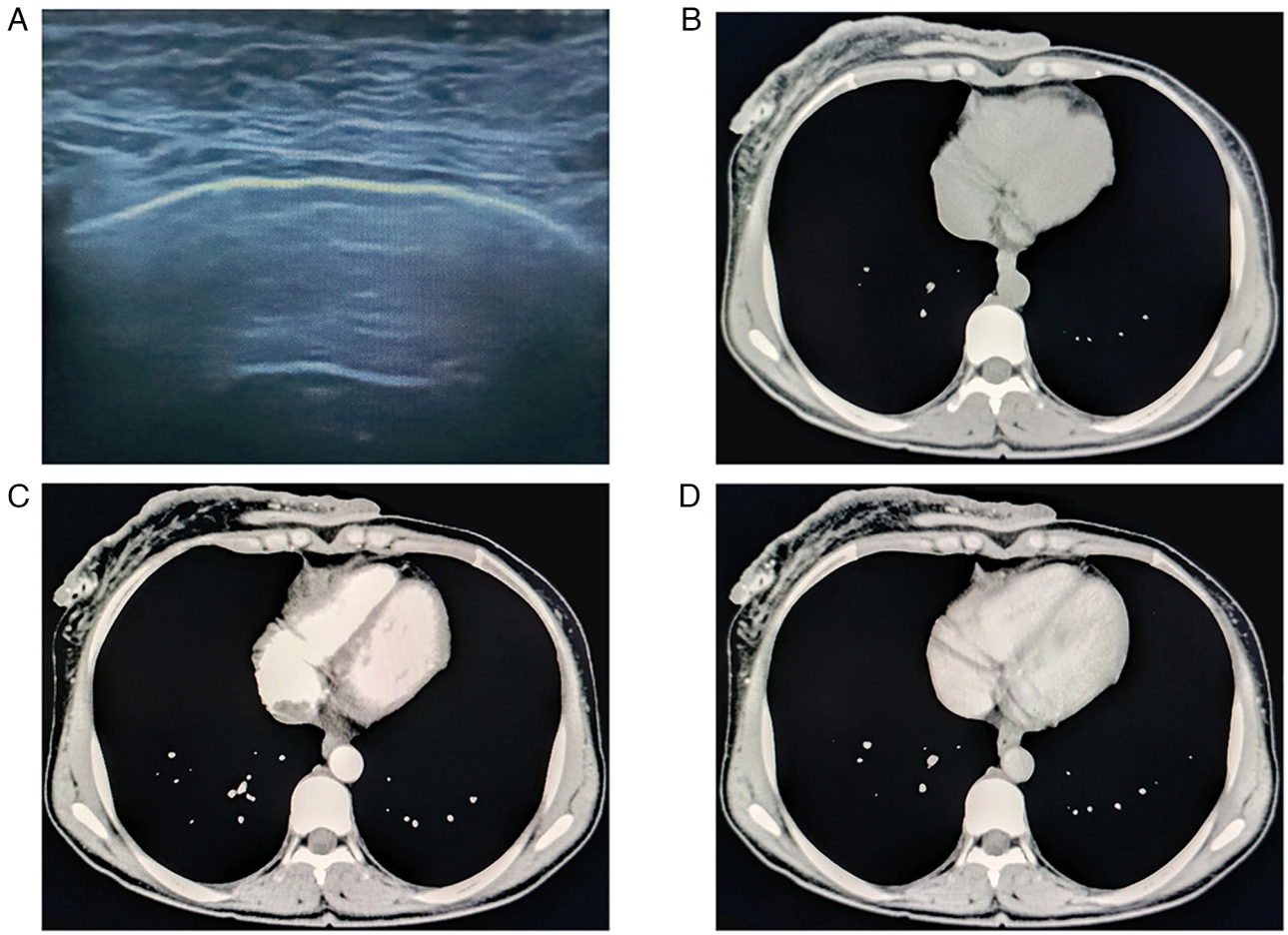

Figure 5. Typical ultrasonic image and CT scans. (A) Ultrasonic image. (B) CT contrast. (C) CT artery phase. (D) CT venous phase.

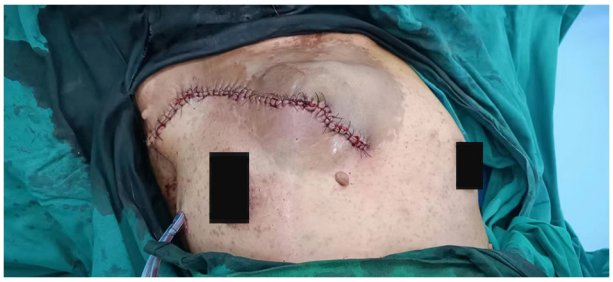

Figure 6. Postoperative anterior image showing a 30-cm incision.

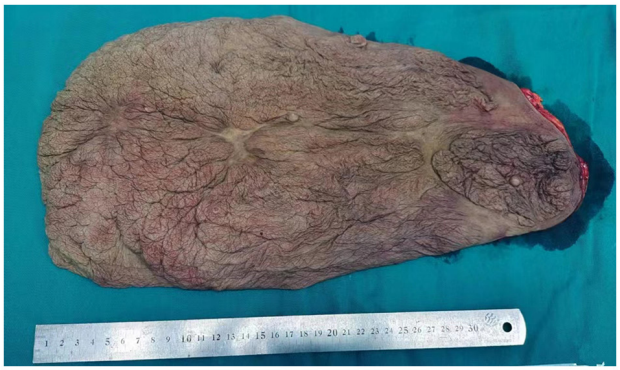

Figure 7. Macroscopic appearance of the giant skin mass after surgical removal; the excised mass measured 33x20 cm.

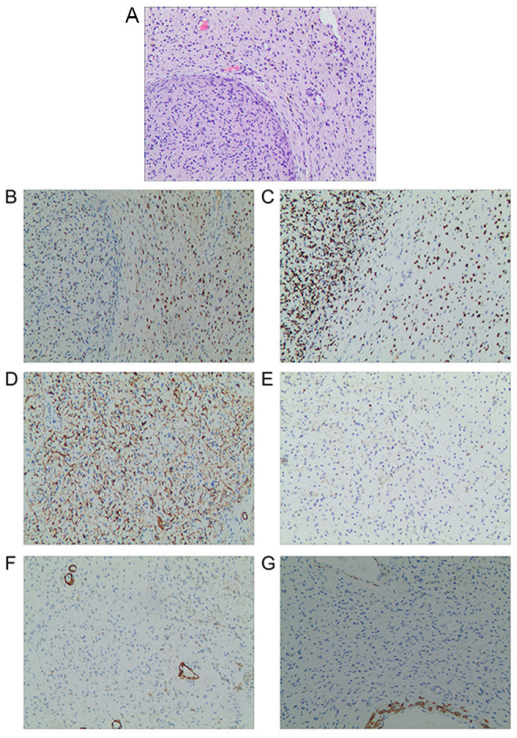

Figure 8. Images from pathological examination (magnification, x10). (A) Tissue morphology (H&E staining). (B-G) Immunohistochemical staining for (B) S-100 (+), (C) SOX10 (+), (D) CD34 (+), (E) Ki-67 (+, <1%), (F) smooth muscle actin (-) and (G) Desmin (-).

Genetic testing is particularly essential for individuals with a familial history of NF1, as it can identify genetic mutations and evaluate the likelihood of transmitting the condition to subsequent generations. The analysis of mRNA and genomic DNA enables the identification of 95% of pathogenic NF1 mutations in individuals meeting the diagnostic criteria established by the NIH (4). Specific correlations exist between mutant NF1 alleles and clinical phenotypes, including whole NF1 gene deletions linked to severe cognitive abnormalities and somatic overgrowth (15,16). Regrettably, the patient did not undergo genetic testing due to financial constraints, although she reported that her daughter exhibits similar manifestations, including cafe-au-lait spots.When contemplating treatment, factors such as patient age, the impact of PN on morbidity or associated risks, as well as growth progression, should be thoroughly assessed. Rapidly progressing PN with potential morbidities may call for intervention, whereas slow-growing tumors with no or minimal impact may warrant observation (17). Surgical intervention and medication are current treatment options for patients with PN. Excision is frequently challenging due to the tumor's impingement on adjacent nerves and structures, as well as its characteristic extensive vascularity that may lead to life-threatening hemorrhage. Personalized treatment plans should be developed through multidisciplinary discussions to optimize benefits and minimize risks (18). In terms of patients who reject surgical treatment or whose tumors are unresectable, annual imaging examination is important in case of transformation to peripheral nerve-sheath tumors, as reported in another rare NF1 case with giant cutaneous neoplasm (6). The patient failed to attend subsequent follow-up appointments at the hospital post-surgery, and thus, it was not possible to monitor the patient's ongoing condition.

In conclusion, the present study reported a case of giant NF1 presented on the right breast skin. We reviewed the choice of diagnosis and therapeutic options for this disease. Family history, multiple café-au-lait spots and cutaneous fleshy nodules throughout the body are the typical characteristics of NF1 (19). Numerous recent advances have been made in the management of PN. In addition to surveillance, symptomatic management and surgery, effective targeted medical therapies have become available. A major challenge going forward will be the identification of individualized treatment schedules and therapeutic combinations that can provide the best outcomes for all patients who require treatment for PN. The clinical implementation of therapies for NF1 requires careful consideration of multiple factors and should be performed with the input of a multidisciplinary team experienced in NF1.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

CZ and YS drafted the manuscript. YL prepared all of the figures and participated in drafting the manuscript. JO conceived the idea of the study and supervised the workflow. CZ and JO checked and confirmed the authenticity of the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The ethics committee at the Affiliated Tumor Hospital of Xinjiang Medical University (Urumqi, China) does not require authors to obtain ethics approval for case reports.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and corresponding images.

Competing interests

The authors declare they have no competing interests.

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