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Non-Ossifying Fibroma Malignantly Transformed Into Fibrosarcoma: A Case Report And Literature Review

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1. Abstract

Non-ossifying fibromas (NOFs) are the most prevalent benign lesions of the developing skeleton. However, the malignant transformation of NOFs is an exceedingly rare phenomenon in clinical practice. To our knowledge, there are no recorded instances in the literature of non-ossifying fibromas undergoing malignant conversion to fibrosarcoma. We present a noteworthy case of a 16-year-old adolescent who presented with a non-ossifying fibroma (NOF) that progressed to fibrosarcoma. The initial diagnosis was suggestive of a malignant bone tumor or tumor-like lesion based on radiographic and computed tomography (CT) imaging, however, histopathology confirmed NOF. However, owing to the patient's clinical symptoms and magnetic resonance (MR) imaging findings, a malignant femoral tumor was suspected. To establish an accurate diagnosis, a post-operative pathological examination was conducted, which confirmed the malignant transformation. Despite subsequent chemotherapy, the treatment was futile. Eventually, a right mid-superior femoral amputation was performed, as the malignant lesion had not metastasized. The patient made a satisfactory recovery and is currently undergoing follow-up. In summary, fibrosarcoma, although rare, can arise as a result of benign conditions such as osteofibrous dysplasia, Paget's disease, osteomyelitis, and NOF, or even metastases that pose a threat to the patient's survival. This case serves as a reminder to clinical surgeons of the critical importance of precision in the diagnosis and management of benign lesions, such as NOF.

2. Keywords: NOF, Fibrosarcoma, Case Report, Malignancy, Amputation Surgery

3. Introduction

Non-ossifying fibromas(NOFs) are a prevalent type of benign fibrous lesions that typically manifest in the long epiphyses of the lower limbs[1, 2]. Historically, NOF was deemed a reactive or developmental anomaly, rather than a bona fide tumor. However, the recent identification by Bovée JV et al. of RAS-MAPK activation in NOF via somatic mutation indicates that NOF should be regarded as a genuine tumor and an integral member of the RASopathy tumor family[3]. In the meantime, A. Rauen has reported that several RASopathies display overlapping phenotypic characteristics and are prone to certain malignancies[4]. Furthermore, the utilization of in situ hybridization has revealed the presence of mutation-positive monocytes in NOF, albeit at low levels[3, 5]. This finding provides evidence that NOF has the propensity to progress into a malignant bone neoplasm. On imaging, nearly all NOF can be diagnosed with confidence based on characteristic X-ray imaging presentations. MRI is seldom required[6], and due to the associated radiation exposure, CT scans are not recommended for younger patients. However, due to the uniqueness of the patient's case, MRI and CT scans were performed, but making a definite diagnosis of NOF malignant transformation into fibrosarcoma based on imaging techniques is a challenging task. The most useful methods appear to be pathological biopsy and genetic testing. Here, we present the case of a 16-year-old adolescent patient who underwent an osteotomy of the right upper mid-thigh and was ultimately diagnosed with NOF malignancy to fibrosarcoma. Currently, the patient is being followed up with no tumor-related symptoms or evidence of tumor progression.

4. Case Presentation

After obtaining informed consent from the patient, we presented a case, On August 15, 2022, a 16-year-old adolescent patient presented to our hospital with right thigh pain for over 4 months. Before this, the patient underwent a local radiographic examination, which revealed an occupying lesion on the lower end of the right femur, possibly a non-ossifying fibroma. After visiting our hospital, the initial radiographic (Figure 1. a, b) demonstrated an irregular area of bone destruction in the right lower femur with a well-defined sclerotic border on the outer edge and an ill-defined inner edge. Furthermore, the CT scan + 3D reconstruction (Figure 1. c, d) revealed an irregularly ground glass-like high-density mass with a periosteal reaction that resembled Codman's triangle. Based on the imaging and presentation, a bone tumor (e.g. osteosarcoma) or a tumor-like lesion (e.g. NOF) was considered. The following day, the patient underwent a puncture biopsy of the lesion in the lower right femur under general anesthesia. Postoperative pathology combined with immunohistochemistry (Figure 1. f-h) confirmed the diagnosis of NOF.
However, plain MR of the right femur with contrast enhancement

showed a soft tissue mass within and around the area of bone destruction in the lower part of the right femur. The T1-weighted image showed uneven signals, whereas the T2-weighted image showed high signals and an obvious layered periosteal reaction, similar to Codman's triangle (Figure 1. e). Due to the mismatch between the first puncture biopsy and the MRI findings before this biopsy, and considering the patient's leg discomfort and the need for further diagnosis, we suspected the presence of malignant tissue within the NOF. Therefore, the patient underwent an open biopsy of a right femoral lesion, and cemented fixation was performed postoperatively. Postoperative pathology (Figure 2. e-i) revealed spindle-shaped tumor cells with abundant density, frequent nuclear division (15-16/10HPF), patchy coagulative necrosis, and tumor invasion of bone tissue, consistent with spindle cell sarcoma. Immunohistochemistry showed CK (-), CD34 (-) Ki67 (60%+), and SMA (focal+). Upon incision of the lesion site, it was found that the lesion had a distinct envelope that was not intact, and it was considered that the malignant lesion might have breached the envelope. Upon scraping the outer layer of the lesion tissue (NOF), necrotic tissue with indistinct boundaries and a grayish-red, fish-like appearance was discovered, confirming the suspicion of malignant transformation within the NOF. Based on current examinations, the diagnosis was right femur spindle cell sarcoma (Enne king IIB stage). To further classify tumor types at the molecular level, we used genetic detection techniques such as NGS and sarcoma RNA fusion detection, which showed malignant transformation into fibrosarcoma accompanied by TERT-TNRC18 and CARD11-BBS9 fusions. Subsequently, the patient was discharged from the hospital after being informed of the above conditions, postoperative imaging results are shown in Figure 2. a-d. The patient and his family came to our hospital again on 10 October for further treatment, combining prior findings with the current MRI (Figure 3. a, b), we then devised a treatment strategy: neoadjuvant chemotherapy + radical surgery + postoperative chemotherapy, and started the first cycle of neoadjuvant chemotherapy on the following day after completing the relevant examinations, and the regimen of neoadjuvant chemotherapy was: isocyclophosphamide + doxorubicin, and we planned to treat the patient with preoperative chemotherapy for 2-4 cycles, and postoperative chemotherapy for 4-6 cycles. However, due to excessive side effects during chemotherapy and poor chemotherapy outcomes, the patient's chemotherapy was terminated in the first cycle. Subsequently, after obtaining the consent of the patient and his family, amputation of the upper middle part of the right thigh was performed on 25 October 2022, after which we removed multiple pieces of diseased tissue, measuring 7.5*5.5*3 cm in size, of which the maximum diameter of the lesion tissue was 5.5 cm, with partial peritoneum attached, and with a greyish hard appearance and greyish-reddish colouring in some areas (Figure 3. c), and send the excised lesion tissue for biopsy (Figure 3. d, e). The results of the current pathology show consistency with Figure 2. e-i. Combined with preoperative MRI (Figure 3. a, b) and Figure 3. c-e, it was found that the malignant tissue and NOF occurred at the same site and the malignant lesion was developed from within NOF, partially breaking through the peritoneum, which reaffirmed the suspicion of malignant lesions in NOF. Therefore, in combination with the results of the genetic test, the diagnosis of NOF was finally confirmed to be osteofibrosarcoma. In this case, the initial punch biopsy failed to obtain malignant tissue due to our error. Fortunately, since this biopsy did not match the MRI results prior to the biopsy, we performed a second open biopsy as well as genetic testing, which ultimately determined that the NOF was malignant as a fibrosarcoma with a partial breach of the envelope. Therefore, to improve the patient's life expectancy, we performed an amputation. Postoperative radiographs (Figure 4) showed good recovery without malignant metastases and related complications, and the patient was subsequently followed up for recovering well.

5. Discussion

[7]The World Health Organization reported a case of osteosarcoma occurring in NOF. Elaine S. Bouttell et al.[8] reported a patient with secondary fibrosarcoma caused by NOF. Subsequently, Biazzo A. et al.[9] reported a case of osteoblastic sarcoma caused by NOF. Picci P et al.[10] reported a series of 12 cases of secondary osteosarcoma originating from benign bone lesions such as GCT, aneurysmal bone cysts, NOF, and simple bone cysts. Due to the long latency of sarcoma development, the authors speculated a "de novo" origin of the neoplasia, possibly due to the use of mesenchymal stem cells in their treatment. In contrast, Takazawa K[11] and Tsuchiya H described cases of fibrous dysplasia and osteosarcoma occurring in the same location. They believed that the malignant transformation of benign lesions is extremely rare but possible. In these cases, it is difficult to determine whether it was originally a sarcoma, as even experienced pathologists find it challenging to accurately distinguish between low-grade fibrosarcoma and fibrous dysplasia.

Fibrous dysplasia (FD) is a prevalent benign fibro-osseous lesion[12]. The occurrence of malignant transformation in FD is exceedingly rare[13-16]. The malignant transformation of FD may be related to Gsα mutations or loss of chromosome 13 leading to RB1 inactivation[17]. As a benign fibrous lesion of the RASopathy tumor family, the reason for the malignant transformation of NOF is still unclear, but it may be related to somatic cell dysregulation and mutations[4, 5, 18]. This patient underwent genetic testing, and based on the results, it was hypothesized that the malignant transformation of NOF in this case might be related to somatic mutations. However, this mechanism still requires further study.

6. Conclusion

In summary, the patient was diagnosed with the infrequent malignant conversion of NOF into fibrosarcoma through imaging and pathological examination. Ongoing follow-up is required based on the patient's current treatment and recovery status.

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