

Case Report

Atypical Neurofibromatous Neoplasm with Uncertain Biologic Potential in the Posterior Mediastinum of a Young Patient with Neurofibromatosis Type 1: A Case Report

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Keywords

Atypical neurofibromatous neoplasm with uncertain biologic potential · Positron emission tomography · Magnetic resonance imaging · Malignant peripheral nerve sheath tumor · Neurofibromatosis type 1

Abstract

Atypical neurofibromatous neoplasm with unknown biological potential (ANNUBP), proposed in a recent NIH consensus overview, is a rare precursor entity of malignant peripheral nerve sheath tumor (MPNST) in neurofibromatosis type 1 (NF1) patients. Only one report on imaging findings of ANNUBP is available. Herein, we present the case of a 19-year-old female, diagnosed with a mediastinal tumor by chance, who visited to our hospital. She had café-au-lait spots on her trunk and a past history of resected neurofibroma. Her family also had café-au-lait spots; therefore, an NF1-induced tumor was strongly suspected. MRI revealed a paravertebral mass of 7.5 cm in size consisting of an inner rim with low T2 signal intensity and an outer rim with high T2 intensity, which was similar to a target sign, adjacent to the pulmonary veins; the center of the tumor was well enhanced by gadolinium, and the peripheral region was myxoid and slightly enhanced. FDG-PET showed high FDG uptake, SUVmax of 8.5, although the peripheral region represented low FDG accumulation. CT-guided needle biopsy was repeated because of the suspicion of an MPNST, which resulted in the histopathological

diagnosis of ANNUBP. Marginal tumor resection was performed, and the final post-resection histopathological diagnosis was ANNUBP transformed from neurofibroma; the region of ANNUBP lost p16 immunostaining, although it was retained in the peripheral region of the neurofibroma. There has been no recurrence or metastasis 1 year after treatment. In conclusion, ANNUBP could be represented as a well-enhanced homogeneous mass on MRI and a high FDG accumulated region on FDG PET/CT, as seen in MPNST, in NF1 patients.

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Introduction

Neurofibromatosis type 1 (NF1) is a developmental and common cancer predisposition syndrome caused by loss of a functional germline mutation in the *NF1* gene [1]. As a life-threatening event, NF1 patients will develop malignant peripheral nerve sheath tumors (MPNSTs), the frequency of which is estimated to occur in 8–16% of NF1 patients [1]. MPNSTs are highly aggressive tumors with 5-year overall survival rate of 20–50% [2]; therefore, early diagnosis and appropriate treatment should be demanded. Plexiform neurofibroma, which typically affects almost any nerve in the body of NF1 patients, grows during early childhood; however, growth arrest in adults and rapid tumor growth in adults should be considered a sign of malignant transformation [3], the mechanism of which is considered to be due to multistep genetic mutation of neurofibroma [4, 5]. As a precursor entity of MPNST, the term “atypical neurofibroma” has been used so far; however, “atypical neurofibroma” is a broad spectrum of pathological entities, and experts’ consensus meeting in 2016 classified the transformation of “atypical neurofibroma” to MPNST into 3 categories: neurofibroma with cytologic atypia or hypercellularity, atypical neurofibromatous neoplasm with uncertain biologic potential (ANNUBP), and MPNST [3]. ANNUBP is pathologically defined by the presence of at least 2 of the following criteria: nuclear atypia, hypercellularity, variable loss of neurofibroma architecture, and/or mitotic activity beyond isolated mitotic figures (>1/50 high-power field and <3/10 high-power field) [3]. Accurately diagnosing ANNUBP and differentiating it from MPNST is important because the former is thought to have low risk of recurrence and metastasis and requires less aggressive resection [6]. There have been many reports on the imaging features and prognostic factors of MPNST [2, 7, 8]. ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) findings were used as tools of detecting malignant transformation from plexiform neurofibroma; however, a discrete cutoff point of SUV_{max} has not been determined [7, 8]. Also, some reports stated that “atypical neurofibroma” could show high FDG accumulation in the tumor [6, 9]; however, ANNUBP is a relatively new and rare entity, and there has been only one report of 3 cases of ANNUBP regarding findings of FDG-PET/CT and preferred treatment strategy [6]. Herein, we presented a patient with mediastinal ANNUBP; FDG-PET/CT findings with high SUV_{max} evoked a differential diagnosis of MPNST; however, magnetic resonance imaging (MRI) findings and multiple sampling with CT-guided needle biopsy of the tumor resulted in a diagnosis of ANNUBP.

Case Presentation

A 19-year-old female presented to our hospital with a suspected mediastinal tumor, which was detected during school physical examination. Fourteen years prior to her first visit, she had undergone resection of a neurofibroma in the abdominal wall. She had café-au-lait spots

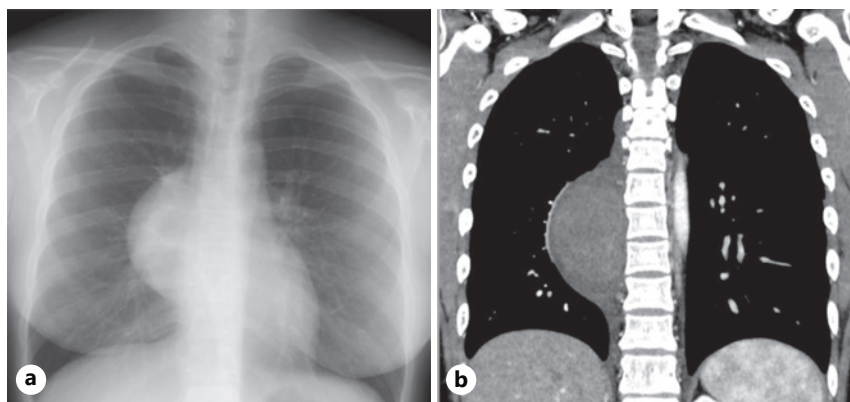


Fig. 1. **a** Chest X-ray shows a well-defined mass lesion in the right paravertebral region of the 6th to 9th thoracic vertebrae. **b** Contrast-enhanced computed tomography shows a right posterior mediastinal tumor with weak central enhancement in the early phase.

on her back and right shoulder and multiple subcutaneous masses on her back. Her mother and maternal grandmother also had café-au-lait spots; thus, tumor caused by NF1 was strongly suspected.

Chest X-ray revealed a well-defined mass lesion in the right paravertebral region of the 6th–9th thoracic vertebrae (Fig. 1a). Contrast-enhanced CT revealed a paravertebral tumor in the same region with a weak diffuse contrast enhancement, without bone invasion into the vertebral body (Fig. 1b). MRI showed a well-demarcated mass of 7.5 cm in size with isosignal intensity on T1-weighted imaging and a slightly high-signal intensity circumscribed mass with a peripheral high-intensity region on T2-weighted imaging. T1-weighted images with gadolinium enhancement depicted a well-enhanced central region of the mass; however, the peripheral region was only slightly enhanced, like a target sign (Fig. 2a–d). There was no necrotic region in the tumor. The medial side of the tumor was in contact with the pulmonary veins and vertebral body, but there was no obvious invasion or destruction. Based on these findings, a benign lesion was suspected. However, FDG-PET/CT depicted homogeneous FDG accumulation in the tumor with maximum standardized uptake values (SUVmax) of 8.6 in the central region and low FDG accumulation in the peripheral region (Fig. 2e). FDG-PET/CT also revealed other lesions; tumors at the left axillary region with SUVmax of 3.0 and cutaneous region of the right buttock with SUVmax of 3.5 were identified, which were possibly neurofibromas. CT-guided needle biopsy was performed, which led to a pathological diagnosis of ANNUBP. However, the possibility of MPNST could not be ruled out because of high FDG accumulation in FDG-PET/CT; furthermore, tumor heterogeneity could exist and single sampling could not diminish the possibility of MPNST. After a multidisciplinary conference, we planned excision with preoperative radiotherapy in case of MPNST and marginal resection in case of ANNUBP. Therefore, a second CT-guided biopsy was performed; five biopsies were performed in total, including tumor margins and centers. Finally, all samples were pathologically diagnosed as ANNUBP, and tumor marginal resection was performed. The tumor was smooth, covered with mediastinal pleura, and was distributed in the T4–9 of the right sympathetic nerve trunk. The tumor was divided and the 5th–8th nerve roots and sympathetic nerve trunk were cut at the level of T4–9 from the inside of the capsule, and the tumor was removed. Histopathological examination of the resected tumor revealed nuclear atypia, high cellularity, loss of neurofibroma architecture, and few mitotic activities; there was no necrosis (Fig. 3a–c). Immunostaining was positive for SOX10 and negative for CD34 and p16 (Fig. 3d); there was no loss of H3K27me3. In the peripheral region, CD34 and

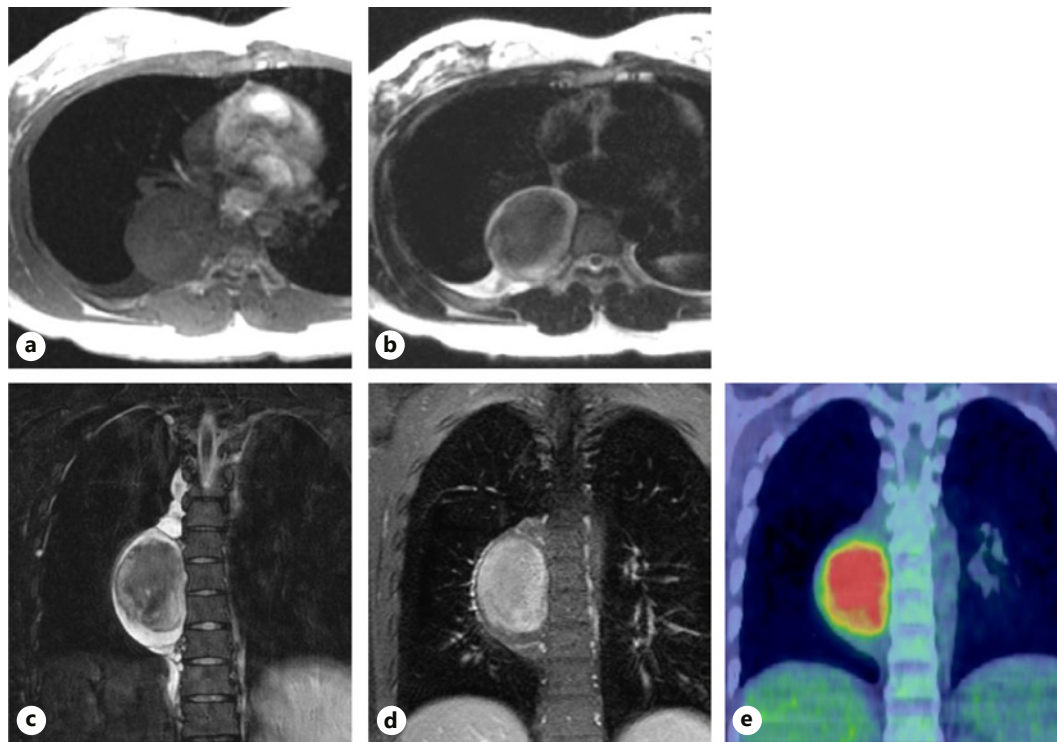


Fig. 2. Axial view of (a) T1-weighted and (b) T2-weighted images shows a mass consisting of an inner rim with low T2 signal intensity and an outer rim with high T2 intensity; coronal view of the (c) short TI recovery image and (d) T1-weighted gadolinium-enhanced image shows a mass that is continuous with the cranial and caudal region. Most of the tumor in the center shows slight high intensity on T2-weighted imaging and good enhancement by gadolinium on T1-weighted imaging. In contrast, the peripheral region of the tumor (arrowhead) depicts high-signal intensity on T2-weighted imaging and is slightly enhanced by gadolinium on T1-weighted imaging. $e^{18}\text{F}$ -FDG-PET/CT demonstrates FDG accumulation in the center of the tumor with an SUVmax of 8.6; the peripheral region of the tumor has low SUV accumulation.

p16 positive spindle cell with low cellularity and no atypia were seen (Fig. 3e, f). These findings fulfilled the criteria of ANNUBP arising from neurofibroma; thus, we did not administer additional treatment. No recurrence was observed, and the left axillary and right buttock masses were stable 1 year post-surgery.

Discussion

Early and accurate detection and management of malignant transformation of neurofibroma in NF1 patients are important but challenging. In 2016, ANNUBP was proposed as tumors that have been inconsistently diagnosed (atypical neurofibroma, low-grade MPNST) and tumors with atypical features that do not meet the pathological diagnostic criteria for MPNST [5]. Although a few reports on “atypical neurofibroma,” which include a broad spectrum of the histopathological consequence of the transformation of neurofibroma to MPNST, have been presented, nothing is known regarding the correlation between the histopathological diagnosis and clinical features of ANNUBP [6, 9]. Our study reported the imaging characteristics of ANNUBP, especially high FDG uptake like MPNST. Preoperative MRI findings and needle biopsy with multiple sampling from the tumor resulted in a diagnosis of ANNUBP arising from neurofibroma; thus, aggressive treatment for MPNST was avoided.

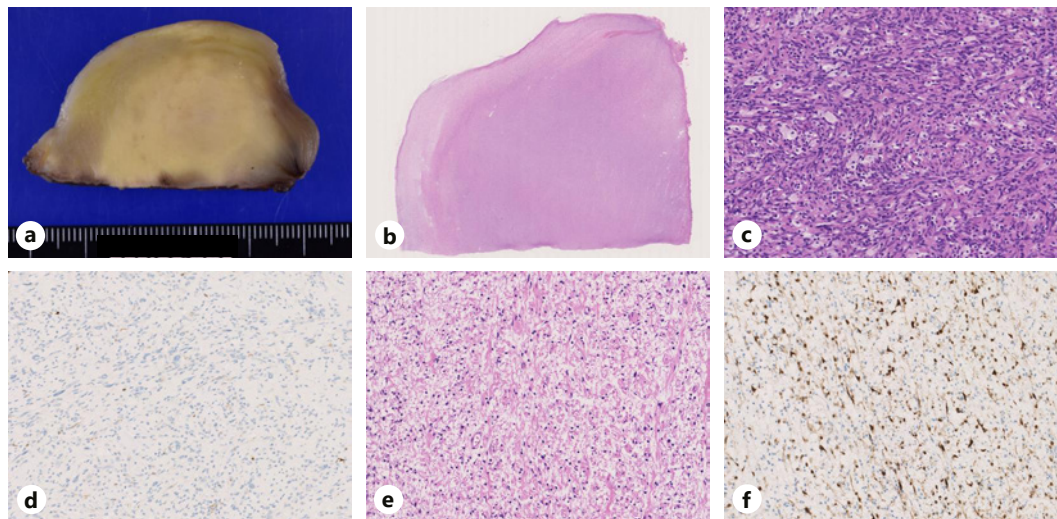


Fig. 3. **a** Macroscopic appearance of the resected tumor shows a glossy peripheral region and a yellowish-white central region. **b** A loupe image of hematoxylin and eosin (HE) staining represents the central part of the tumor with high cellularity. **c** Microscopic image of H&E stain of the central region of the tumor shows tumor with nuclear atypia, high cellularity, loss of neurofibroma architecture, and **(d)** loss of p16 expression. **e** Microscopic image of H&E stain of the peripheral region of the tumor shows **(d)** interlacing bundles of elongated cells with thin wavy nuclei in the edematous matrix with interspersed collagen bundles and **(f)** tumor cells with retained p16 expression.

Transformation of neurofibroma to MPNST in NF1 patients has a dismal prognosis [2]; early and accurate detection of this malignant transformation is challenging in the management of NF1 patients. There have been many analyses regarding the best imaging modality for detecting malignant transformations of neurofibromas; among them, FDG-PET/CT has been reported to be useful, and some reports have proposed a SUVmax cutoff value between 3.5 and 7.48 for MPNSTs in cases of NF1 to differentiate MPNSTs from neurofibromas [7, 10]. However, as a limitation, there was a significant overlap in the SUVmax between neurofibromas and MPNSTs, and ANNUBP has been reported to have a higher FDG avidity than neurofibromas [6]. Compatible with this report, FDG-PET/CT revealed high FDG accumulation (SUVmax: 8.6) in our case. According to the analysis of FDG avidity and genetic alterations in head and neck squamous carcinoma, genetic alteration of *CDKN2A* was associated with high FDG uptake, which is possibly related to the cell cycle dysregulation associated with *p53* [11]. ANNUBP is thought to be associated with the homozygous loss of *CDKN2A* [3]; part of the ANNUBP in our case represented p16 loss in IHC, which could be a reason why ANNUBP has FDG avidity. As another imaging modality, MRI has been reported useful in differentiating MPNST from neurofibroma [8, 12, 13], despite existence of some overlapping as in FDG-PET/CT. In cases of MPNST, intra-tumoral cystic lesions have been reported, as well as MRI characteristics such as heterogeneity on T1-weighted imaging, a peripheral enhancement pattern, and a perilesional edema-like zone [13]; however, these findings were not observed in our case, suggesting that the possibility of MPNST was low. Combining FDG-PET/CT with MRI could be useful for diagnosing atypical and malignant transformations of neurofibromas; however, at present, it can be difficult to distinguish malignant transformation only by imaging findings, and thus early histopathological confirmation is more important.

The first CT-guided biopsy revealed a histopathological diagnosis of ANNUBP. Recent genomic study revealed that some histological and genomic heterogeneity could exist in a single nodule [14]. High FDG avidity made us suspect MPNST; thus, we performed a second

CT-guided biopsy from five sites, including the marginal and internal sites. The results were same as the first biopsy, with histopathological diagnoses of ANNUBP. Without doubt, multiple sampling cannot reflect whole tumor heterogeneity; thus, multiple sampling should be considered in case of distinct nodular lesions of NF1 patients to avoid repeated procedures.

Recommended treatment for ANNUBP is resection before malignant transformation [3]. The appropriate surgical margin for ANNUBP is unknown. A recent study of atypical neurofibroma revealed that no recurrence was observed after marginal resection [6]; however, the observation period after surgery was relatively short, median of 2.45 years; thus, clinical outcome with long-term follow-up is required. With precise histopathological analysis differentiating “atypical neurofibroma” into a precise category, we hope that more cases will be accumulated in the future for evaluation of the clinical course and treatment of ANNUBP.

Conclusion

We experienced a case of mediastinal ANNUBP with high FDG accumulation. Preoperative MRI findings and multi-sampling by needle biopsy diagnosed the tumor as ANNUBP; thus, intensive treatment for MPNST was avoided. The clinical significance of these findings regarding the imaging findings and proper treatment strategy of ANNUBP for management of NF1 patients requires additional study. Furthermore, as an emerging technology, liquid biopsy, which can detect circulating tumor DNA, could have a potential role in early and noninvasive diagnosis of malignant transformation [15].

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study was approved by Research Ethics Committee of the Faculty of Medicine of the University of Tokyo (approval number 11019).

Conflicts of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author Contributions

Kodai Miyamoto, Liuzhe Zhang, and Hiroshi Kobayashi wrote the paper and performed the literature review. Yusuke Tsuda, Naohiro Makise, Yoichi Yasunaga, Masako Ikemura, Yudai Nakai, Eisuke Shibata, Tetsuo Ushiku, and Sakae Tanaka contributed to the conception and design of the manuscript and critically revised the manuscript. The following authors discussed the case at a multidisciplinary cancer board conference: Naohiro Makise, Yoichi Yasunaga, Masako Ikemura, and Tetsuo Ushiku, who contributed to the pathological diagnosis; Yudai

Nakai and Eisuke Shibata, who contributed to the imaging diagnosis and image-guided intervention; and Kodai Miyamoto, Liuzhe Zhang, Yusuke Tsuda, Hiroshi Kobayashi, and Sakae Tanaka, who contributed to the decisions for the treatment strategy and surgical treatment. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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