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Case Report

From detection to disappearance: A tale of a nodule

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A B S T R A C T

Spindle cell lesions span from benign to aggressively malignant, the most concerning being the carcinoma, sarcoma, and melanoma species. While spindle cell carcinoma is the most common spindle cell lesion found along the upper aerodigestive tract (UADT), it only accounts for <0.5 % of pulmonary malignancies [1,2]. We present an adult male admitted for chest pain, who was found to have a malignant left upper lobe (LUL) spindle cell neoplasm. Three pathology departments preformed immunohistochemical analysis on various tissue specimens, searching for a speciated diagnosis, highlighting the importance of advanced immunostains for the diagnosis and subsequent treatment of these difficult lesions.

1. Introduction

Benign versus malignant is the most crucial differentiating characteristic of any disease process, and one of the hardest declarations to make when dealing with spindle cell neoplasms. Spindle cell, or sarcomatoid, lesions encompass greater than 16 classes of non-neoplastic, benign, and malignant lesions of the UADT, and to date differentiating between these subtypes of spindle cell lesions poses a significant challenge for physicians across subspecialties [1]. This diagnostic dilemma often results in excessive treatment regimens or malignancy misdiagnosis. With limited literature available on pulmonary spindle cell lesions, advanced immunohistochemical (IHC) analysis is crucial for diagnosis with prompt and efficacious treatment plans for our patients. This case utilized three pathology labs for analysis, ran close to 30 immunostains, and finding a clear diagnosis for this malignancy was still quite difficult. Sharing more cases of such a rare disease can hopefully help close knowledge gaps, allowing for more targeted diagnosis and successive treatment.

2. Case report

A male in his late 60's with a history of thyroid follicular adenoma status post radiation and thyroidectomy (2004), spindle cell sarcoma of the scalp status post resection (2021), and melanoma of the shoulder status post resection (2023) presented to the hospital with chest pain, dyspnea, and diaphoresis with a 25 lb weight loss over the past two months. He was a nonsmoker, without significant environmental exposures. Work up with chest imaging revealed a new 2 cm LUL non-spiculated bilobed rounded pulmonary nodule, shown in Fig. 1. One month later the patient underwent a robotic electromagnetic navigational bronchoscopy with transbronchial fine needle aspiration (FNA) and cryobiopsy, diagnostic for a spindle cell neoplasm. Endobronchial ultrasound scanning was performed noting one enlarged hilar lymph node, station 11L, that was negative for malignancy on 4 FNA passes. Initial IHC stains, shown in Figs. 2 and 3, showed spindle cell proliferation of intermediate cells, favoring a malignant peripheral nerve sheath tumor or synovial sarcoma. Specimens were then sent to a specialized tertiary center for a second read, resulting as an atypical spindle cell neoplasm, favoring metastatic melanoma or cellular schwannoma.

Initial staging imaging was performed. Brain MRI was negative for signs of metastasis. A full body PET scan was notable for a 4.3 × 2.9 cm LUL mass, PET avid with SUV 17.7, and an enlarged 11L lymph node, PET avid with SUV 17.7. No signs of distant

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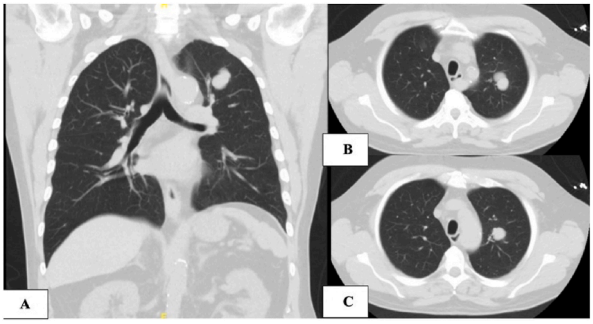

Fig. 1. 1A: Chest CT sagittal view with a LUL non-spiculated apicoposterior nodule
1B, 1C: Chest CT axial view demonstrating the bilobed nature of the apicoposterior LUL nodule.

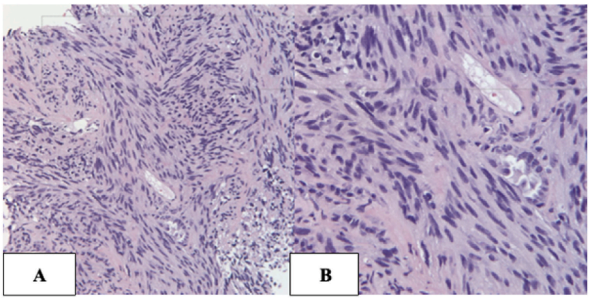

Fig. 2. 2A,2B: Bronchoscopic cryobiopsy tissue showing hypercellular spindle cell proliferation with a vaguely nested architecture with moderate pleomorphism and ample cytoplasm arranged in bundles/fascicles.

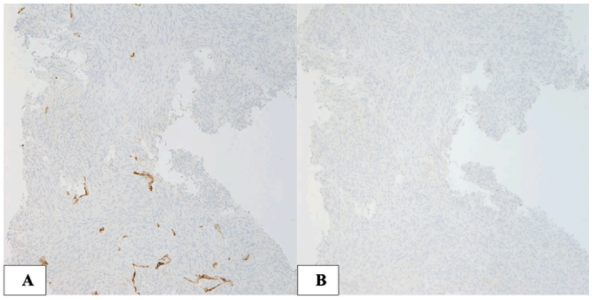

Fig. 3. 3A: Bronchoscopic cryobiopsy EMA stain negative
3B: Bronchoscopic cryobiopsy p63 stain negative.

metastasis were noted on the full body PET scan. Three months after initial presentation, the patient underwent a LUL resection and excisional lymph node biopsy with a final pathology report of high grade sarcomatoid neoplasm and once again, a negative lymph node. With lobectomy being the optimal intervention in most early-stage non-small cell lung cancers (NSCLC), our patient underwent treatment for what we believed to be a stage 1B NSCLC. In stage 1 disease, adjuvant chemotherapy and radiation treatment is not typically indicated, however given the concern for high grade malignancy and potential for metastatic disease, the patient has been in the care of radiation oncology with an aggressive treatment plan including potential chemoradiation [4,5].

3. Discussion

Spindle cell lesions are known to occur most often at mucosal sites, along the skin and soft tissues of the head and neck, and along the UADT. They are often quite difficult to distinguish from one another, which can be distressing as the spindle cell lesions range from benign to reactive, and aggressively malignant. While clinical and radiographic evidence is always taken into consideration, spindle cell lesions rely often on histologic data for diagnosis [1]. Our patient had IHC performed on his bronchoscopic tissue and surgical lobectomy tissue. Numerous IHC stains were run without a clear subclassified diagnosis, fostering the question, what type of sarcomatoid malignancy is this? Primary carcinoma, malignant melanoma, and malignant sarcoma were all possible in our patient given his dermatologic malignancy history.

The most common of the pulmonary spindle cell, or sarcomatoid, lesions, is spindle cell carcinoma, however it still only accounts for <1 % of all pulmonary malignancies. Based on the Surveillance, Epidemiology, and End Results (SEER) Database, of all non-small

cell pulmonary malignancies diagnosed between 1973 and 2013, spindle cell carcinoma made up about 0.5 %, with rates as low as 0.3 % having been recorded in literature [1–3,7]. With a known pulmonary spindle cell neoplasm, and staging scans negative for signs of metastatic disease, the highest diagnostic likelihood would be spindle cell carcinoma in our patient, however a lack of expected pathologic staining patterns resulted in several subspecialists scratching their heads on a diagnosis in this patient.

Lymph node sampling, PET imaging, and MRI imaging were all performed, and subsequently negative in our patient, making a metastatic spread of disease quite difficult to conclude. We had to further rely on histopathologic analysis. The most common of the spindle cell lesions, spindle cell carcinoma, is a variant of squamous cell carcinoma, with epithelial pleomorphic, or spindled cells [1]. As seen in Fig. 2, the tissue sample from our patient clearly showed spindle cell proliferation with polymorphism. Epithelial differentiation via IHC staining is felt to be the defining confirmation in spindle cell carcinoma when positive, however it is not a sensitive factor and a lack of staining, cannot rule it out. With the most common epithelial stains including AE1/AE3 + CAM 5.2, EMA, and p63, research from Lewis et al. found that only 79–81 % of spindle cell carcinoma cases were positive for a single one of these markers [1]. The tissue in our patient's case was run through close to 30 immunostains, with all the epithelial stains being negative, as seen in Fig. 3. His tissue did stain positive for SOX10 and S-100, two neural crest-derivative stains. Schwannian and melanocytic tumors have often stained positive for SOX10 and S-100, leading to several "favored diagnosis" in our patient's pathology reports and further obviating the ability to rule out even more peculiar diagnosis than the carcinoma species we initially were suspicious for [6]. Our initial differential diagnosis remained quite large when looking solely at the inconclusive data we obtain from the IHC analysis, which pushed us to look further at clinical markers to hopefully guide our patient's workup and treatment.

Aside from IHC data, clinical associations are starting to prove helpful in diagnosing these difficult lesions, with the majority of current data relating to spindle cell carcinomas in particular. Looking at risk factors, spindle cell carcinomas have been found to have a high correlation with smoking, recorded rates being as high as 96.6 % [9]. Similarly, radiation exposure has steaked its association with spindle cell carcinoma. Prior to 2010, a cohort of 326 cases of spindle cell carcinoma were evaluated, combined from five separate studies, and 18 % of all cases occurred in areas of the body that had been previously exposed to radiation treatment within the past 7–16 years. This compares to the more well known, 1 %, of all squamous cell carcinomas occurring at sites of prior radiation. Our patient has a known history of follicular adenoma, status post radiation treatment to the neck in 2004, placing him at the nine-year mark post radiation, with his apical lung lesion located near the prior radiation site.

Over time, radiographic correlated characteristics have also been noted with spindle cell carcinoma lesions, however the data remains sparce. The first noted characteristic seen in several of these lesions is a multilobed nature of the spindle cell carcinoma. Our mass, as seen in Fig. 1 appeared biolobed [1]. Interestingly, our patient also had quite intense PET avidity on his staging scans. A retrospective study conducted by Roesel et al. discovered that pulmonary sarcomatoid lesions were found to have on average SUV's of 14.3 ± 3.1, which is notably higher than other NSCLC [9]. Our patient's lesion falls within these parameters scoring an SUV of 17.7. These correlations relate solely to spindle cell carcinomas as radiographic and clinical data for other types of spindle cell lesions is severely lacking. No clear associations are known at this time. Given our limited knowledge, this patient's clinical risk factors and lesional characteristics, along with a lack of clear metastatic disease, pulmonary spindle cell carcinoma rose higher on our differential diagnosis.

After tissue diagnosis of NSCLC, staging of such rare lesions is exceptionally important. Our patient underwent workup with an EBUS, excisional lymph node biopsy, brain MRI and PET scan, all of which turned up negative for clear signs of metastatic disease. He was urgently referred to hematology oncology while diagnostic tests remained pending, given the concern for high grade malignancy. With limited knowledge about these lesions, treatment guidelines remain congruent with treatment for other NSCLC. Stage 1a and 1b lesions should be surgically resected, if possible. Our patient underwent a LUL lobectomy less than 3 months after diagnosis. There is debate on the use of adjuvant radiotherapy in resected early-stage NSCLC. A metanalysis of 9 randomized trials looking at adjuvant radiotherapy in resected stage I-III disease was cited in the European Respiratory Journal guidelines, revealing an absolute detriment of 7 % increased 2-year mortality with the largest adverse effect being allocated to those with stage I or II disease [10]. Therefore, radiotherapy is typically reserved for post-operative patients with positive surgical margins or higher disease stages [4]. In our case, chemoradiation was considered given the risk of high-grade malignancy and lack of treatment guidelines. Fig. 4 shows the treatment algorithm that our patient underwent. With spindle cell lesions being so difficult to diagnose and often being high-grade malignancies, treatment regimens are frequently more aggressive than our typical NSCLC guidelines recommend, further emphasizing the importance of improved diagnostic resources.

Our patient has not finished his extensive journey. With the 5-year survival rate of sarcomatoid lung cancers being approximately 20 %, our patient has started an aggressive treatment regimen [7]. As of 2018, there were only 13 reported cases in literature of the most common of these malignancies, spindle cell carcinoma, emphasizing the importance of reporting these cases to share the limited knowledge that we have [8]. It is imperative to continue growing our expertise on both the malignancy itself, and the IHC associated, to master the diagnosis of such a detrimental disease and potentially spare patients' complications and aggressive treatment.

4. Conclusion

- Malignant pulmonary spindle cell lesions are exceedingly rare and retaining a high clinical suspicion is imperative for improved diagnosis and patient outcome.
- There is an exceptional need for advanced immunohistochemical analysis, as it is often the only source of clear diagnosis in these poorly differentiated cases.
- Early referral to hematology oncology, surgery, and radiation oncology is crucial for early treatment

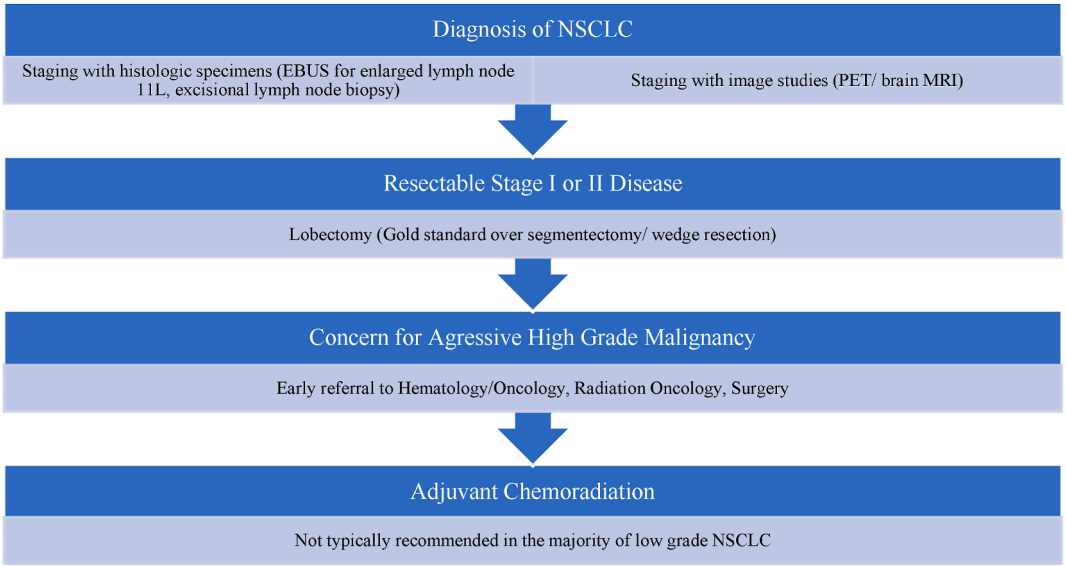

Fig. 4. The individualized management algorithm of our patient for high grade NSCLC.

CRediT authorship contribution statement

Rachel Herr: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Himmat Grewal:** Supervision, Conceptualization. **Ramsy Abdelghani:** Supervision, Conceptualization.

Declaration of competing interest

None.

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