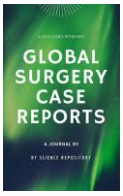

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Case Report & Literature Review

Underestimating the Burden of Disease in Sarcomatoid Carcinoma of The Lung: A Case Report and Literature Review

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ABSTRACT

Acute appendicitis is one of the most common emergency surgical procedure, yet atypical presentation sometimes can be challenging for clinician. I present a case of 19-year-old gentleman that initially presented with 1day history of bilateral testicular pain and lower abdominal pain. His past history includes a positive sexual history. Initial ultrasound of the testis showed bilateral orchitis and an equivocal appendix. With a significantly raised inflammatory marker and highly suspicious for appendicitis, a CT scan was obtained which showed perforated appendicitis and the patient underwent laparoscopic appendicectomy with resolution of symptoms after that. We encourage clinician to be aware of this clinical pitfall as patient can sometimes be managed in other department to minimise any delayed diagnosis or any unnecessary procedure.

Background

Sarcomatoid carcinomas of the lung (SCL) are characterized by a malignant mesenchymal component concurrent with a malignant epithelial component [1]. Sarcomatoid carcinomas are rare, aggressive tumors, accounting for less than 1% of all primary pulmonary neoplasms, often diagnosed at advanced disease stages, portending a poor prognosis [1, 2]. It is not unusual for patients to present with synchronous metastases at the time of initial diagnosis. However, reported rates of gastrointestinal metastases are quite rare but should be considered in this patient population.

Case presentation

In 2017, a locally advanced sarcomatoid carcinoma was diagnosed in a 57-year old man (Figure 1). He presented with anemia and melena and was initially diagnosed with a gastric ulcer. The patient had an elevated Prostate Specific Antigen (PSA) and upon further imaging by Positron Emission Tomography (PET) scan, was found to have three lesions: a largely necrotic PET-avid lesion in the left upper lobe of the lung, and two areas of PET avidity in the small bowel (Figure 1).

Subsequently, the patient was taken to the operating room and found to have multiple (>10) foci of hyper-pigmented lesions in the small intestine (Figure 2). One lesion appeared to be responsible for events of intermittent intussusception, which likely contributed to his anemia and the two larger lesions, which likely correlated with the PET scan findings, were excised via segmental bowel resections. However, multiple other lesions observed intraoperatively were not observed on the PET scan and emphasize how the true disease burden was underappreciated preoperatively. To determine if these lesions were metastases, histopathologic analysis identified a markedly pleomorphic dyshesive neoplasm displaying atypical mitotic figures (Figure 3). Furthermore, immunohistochemistry of the small bowel segments were found to be diffusely positive for p63 and focally positive for pancytokeratin OSCAR, pancytokeratin AE1/AE3, and EMA staining, while negative for caudal-related homeobox 2 (CDX2), cytokeratin 20 (CK20) and desmin. These findings in the staining pattern of the lesions were consistent with the primary lung biopsies, confirming metastatic sarcomatoid carcinoma. Following the surgery, the patient recovered well and was subsequently treated with 3850 cGy of palliative external beam radiation over 2 weeks to his left upper lobe lesion followed by seven cycles of carboplatin and paclitaxel and most recently seven cycles

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of pembrolizumab. The patient is currently alive with disease and his most recent scan demonstrates stable disease for 13 months after bowel resection.

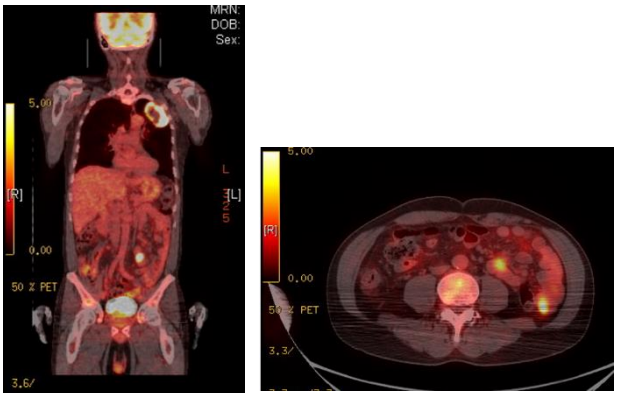

Figure 1: PET scan demonstrating PET avidity of nodules in the abdomen on coronal **(a)** and axial **(b)** slices.

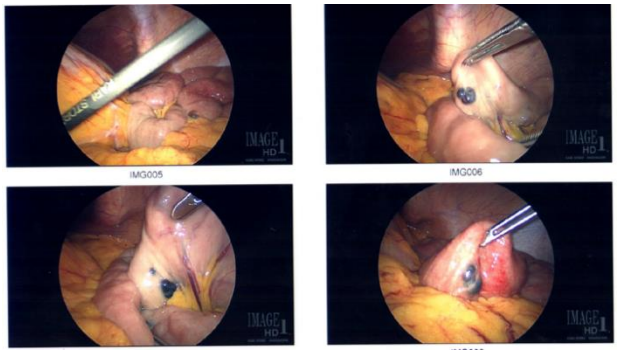

Figure 2: Laparoscopic findings of surgery demonstrating pigmented nodules on multiple areas of small bowel **(a)** and resection specimen where hemorrhoage had occurred **(b).**

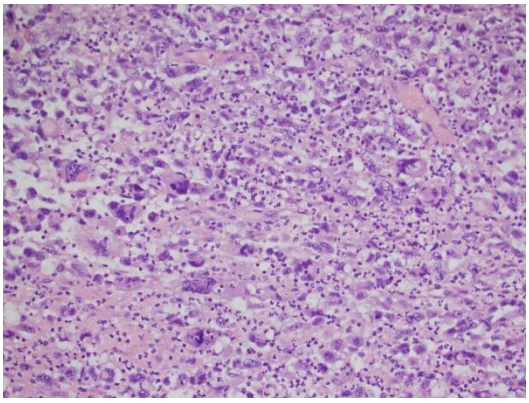

Figure 3: H&E slide of tumor specimen.

Discussion

This case highlights the occult nature of gastrointestinal metastases in sarcomatoid carcinomas of the lung (SCL). On the PET scan, there were only 2 areas of observed uptake (Figure 1b); however, following diagnostic laparoscopy, greater than 10 deposits of tumor were evident in the small bowel, with diameters that were certainly large enough for PET to detect (Figure 2). Overall, sarcomatoid carcinomas of the lung compose 0.2-0.4% of all primary pulmonary neoplasms [2, 3]. The tumor most often presents as a solitary mass that sits in the upper lobes [4]. SCLs are generally thought to be more aggressive and have a worse prognosis than ordinary lung carcinomas [5, 6]. In a propensity matched model, 63 patients were compared to 62 patients with non-small cell lung cancer (NSCLC) and the 5-year survival for SARC was 24.5% compared to 46.3% in the NSLC group. After resection the median time to recurrence was 11.3 versus 61.4 month [5]. This poor prognosis persists even in Stage I disease, whereby the 5-year survival in SCL was 16.3%, in NSCLC 81.8% and in squamous cell carcinoma was 70.2% [7].

Table 1: Common Sites of Metastases in SCL Patients.

Study (Author/Year)	Age	Male/Female	Metastasis Locations	Symptoms	Imaging Methods	Resection (Y/N)	Subsequent Treatment (Y/N)
Arshad et al., 2017 [33]	63	M	Spine	Back pain, cough	CT scan, MRI	Spine mass removal and laminectomy, no resection of lung mass	Gemcitabine/Carboplatin; biphosphonates for bone metastasis
Takeda et al., 2016 [34]	65	M	Trachea	Hemosputum	CT Scan, bronchoscopy	Unresectable	Carboplatin, paclitaxel plus radiotherapy
Le et al., 2016 [35]	79	M	Upper lip, two intracranial lesions	1 month persistent cough	X-ray, CT scan	Incisional biopsy	Palliative radiotherapy
Romano et al., 2015 [36]	60	M	Intestinal, omental, liver	Chest pain, hemotypsis	CT scan	Small bowel resection	None
de Oliveira et al., 2013 [37]	61	F	Brain	Cough, hemophtysis, fever	CT scan, x-ray, bronchoscopy	Pulmonary lobectomy, microsurgery for resection of brain lesion	None

In this context and due to the lack of effective systemic therapy and the resistance to radiation, surgery is often the preferred modality for primary SCL [8]. Table 1 presents a summary of case reports that have presented a broad spectrum of metastatic locations, with the most common sites of extrapulmonary metastasis being the brain, bone, adrenal glands and liver [9]. The incidence of gastrointestinal metastases is 5-14%, with the small bowel being the most prominent location [4]. Patients who suffer from gastrointestinal metastases in this disease primarily present with melena, abdominal pain, and signs and symptoms of intermittent obstruction in the context of intussusception [9]. However, SCL patients who suffer from small bowel metastasis particularly may present asymptomatically, with the progression later being revealed through perforation, obstruction, or gastrointestinal bleeding [10]. Incidences of secondary metastasis, especially those that present at later stages due to the lack of initial symptoms, require surgical intervention in almost every case as intestinal intussusception is known to cause bowel obstruction, intestinal necrosis, and bleeding [11]. As demonstrated in this case report, the nature of these metastatic deposits can be often difficult to detect and therefore in the context of symptoms, there should be a particularly low threshold of concern for further imaging or workup. Imaging to detect metastases is most commonly in the form of PET scans or CT scans, however as demonstrated in this case, the burden of disease can be underestimated. In patients with primary carcinoma of the lung with gastrointestinal metastases, McNeill et al have reported an average of 4.8 metastatic sites, which can allow for a substantial underestimation if the burden of disease is not fully appreciated through cross sectional modalities [12].

SCL most often presents with a biphasic histology, concerning both epithelial and mesenchymal characteristics. The biphasic characteristics are comprised of a component of NSCLC that is intermingled with a sarcomatoid component (formerly pleomorphic carcinoma) or with heterologous sarcomatous tissue (formerly described as carcinosarcoma) [7]. Under the umbrella of sarcomatoid carcinoma of the lung, pathological characteristics have further characterized various subtypes of the disease, which are pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma [13-15]. Staining characteristics of this disease include CK7+ consistent with an epithelial component, and vimentin, signifying mesenchymal differentiation [16]. Tumors can also be positive for TTF-1, alluding to their pulmonary origin [4].

In early stage operable SCL patients, surgical intervention remains the standard of care among candidates and has proven to produce the greatest overall survival benefit [17, 18]. In a retrospective study at the University of Cincinnati Medical Center (UCMC), Karim et al. demonstrated an overall survival of 713.5 days, or 23.5 months in patients that underwent surgery, a sentiment that has been widely consistent with various other institutional studies conducted [17]. Furthermore, the aforementioned study explored overall survival of SCL patients when chemotherapy treatment was accounted for as the study stated that patients who underwent systemic chemotherapy and surgery had an overall survival of 457.5 days, or 15 months, whereas those who underwent chemotherapy only had an overall survival of only 256 days, or 8.4 months [17].

Table 2: Summary of Cross-Sectional Studies on SCL Patients.

Study (Author, Year)	No. of Patients	AJCC Staging	5-year Survival	Recurrence Rate (%)	Recurrence	Median Survival (months)	Resection (Y/N, %)	Chemotherapy (Y/N, %)
Weissferdt et al., 2017 [38]	86	IA: 5 patients (5.8%) IB: 9 patients (10.5%) IIA: 12 patients (14.0%) IIB: 32 patients (37.2%) IIIA: 22 patients (25.6%) IIIB: 3 patients (3.5%) IV: 2 patients (2.3%) NK 1 patient (1.2%)	34.60%	NR	NR	15	Yes, 100%	Yes, 27% neoadjuvant, 60% adjuvant
Roesel et al., 2017 [39]	58	IA: 4 patients (8.7%), IB: 7 patients (15.2%), IIA: 9 patients (19.6%), IIB:15 patients (32.6%), III: 7 patients (15.2%) IV: 4 patients (8.7%)	28.70%	60.90%	Local: 8 patients Distant:12 patients Both: 8 patients	Stage I: 44.9 Stage II: 14.9 Stage III: 10.2 Stage IV: 5.6	Yes, 79.3%	Yes, 31%
Steuer et al., 2017 [40]	7965	I: patients (18%), II: patients (10%), III: patients (24%), IV: patients (48%)	14.40%	NR	NR	6.4	Yes, 38%	Yes, 39%
Lococo et al., 2016 [41]	148	I: 36 patients (24%) II: 69 patients (47%)	12.6%	70%	Local: 58% of cases Distant: 81% of cases	19	Yes, 100%	Yes, 67%

		III: 33 patients (22%) IV: 10 patients (7%)						
Gu et al., 2015 [42]	95	I: patients (24.2%) II: patients (27.4%) III: patients (31.6%) IV: patients (16.8%)	21%	NR	NR	11.54	Yes, 92.6%	Yes, 37.9%
Mochizuki et al., 2008 [43]	70	I: 23 patients (33%) II: 22 patients (31%) III: 20 patients (29%) IV: 5 patients (7%)	36.7%	58.5%	Local: 29% of cases Bone: 29% of cases Brain: 25% of cases Pleura: 17% of cases Liver: 17% of cases Thorax and Neck Lymph Nodes: 8% of cases Adrenal glands: 8% of cases Stomach: 4% of cases Jejunum: 4% of cases Skin: 4% of cases	23	Yes, 100%	NR
Martin et al., 2007 [5]	63	IA: patients (8%) IB: patients (19%) IIA: patients (0%) IIB: patients (30%) IIIA: patients (22%) IIIB: patients (16%) IV: patients (5%)	24.5%	62.5%	Local: 21% of cases Distant: 51% of cases	17.4	Yes, 100%	Yes, 24% pre-operative chemo
Venissac et al., 2007 [44]	39	IB:15 patients (38.5%) IIB:14 patients (35.9%) IIIA: 7 patients (17.9%) IIIB: 2 patients (5.1%) IV: 1 patient (2.6%)	33%	53.8%	Local: 10 cases Brain: 9 cases Bone: 6 cases Lung: 4 cases Bowel: 2 cases Suprarenal Gland: 1 case	11	Yes, 100%	Yes, 43.6%

Despite surgery being the preferred treatment option for SCL patients with early localized disease, high recurrence rates have unfortunately been reported [19]. Recent cross-sectional studies at various institutions have reported recurrence rates greater than 50% in SCL patients who have undergone surgical intervention, with rates ranging from 53.8% to 70% (Table 2). As seen in this case report, the high incidence rate of recurrence may be attributed to the highly aggressive, occult nature of SCL and the underestimation of the burden of disease through cross sectional imaging. Furthermore, the underappreciation of the burden of disease is accentuated by the fact that the majority of recurrences in SCL surgical patients are distant, rather than local (Table 2). Lococo et al. have reported a distant recurrence rate of 81% in 148 consecutive patients across five institutions, even in 62% of patients who possessed pathological stage I tumors and underwent R0 resections [20]. The underappreciation of SCL may have been a contributing factor to hidden metastatic deposits, which unfortunately led to worse prognostic outcome in surgical patients that had been deemed no evidence of disease (NED) after pathological confirmation.

In spite of the potential for recurrent disease in surgical candidates with sarcomatoid carcinoma of the lung, surgical excision remains the preeminent treatment option as current lines of chemotherapy are ineffective and there are not targeted immunotherapeutic drugs or cancer vaccines for SCL, due to the rarity of the disease [19, 21]. In a cohort study of 56 SCL patients who underwent an R0 lung cancer resection, Chaft et al. demonstrated that there was not a significant difference in disease free probability (DFP) of SCL patients that were deemed stage Ib-IIa; however, there was a benefit seen in patients with IIb-IIIa disease [22]. Vieira et al. further explored the efficacy of first-line chemotherapy in a study with 97 SCL patients that possessed advanced or metastatic disease and showed that there was not a statistical difference between the overall survival of patients receiving or not receiving a platinum-based chemotherapy [23]. Thus, there remains an equivocal response seen in SCL patients at various cancer stages and a need to comprehensively understand the carcinogenesis of the SCL.

Due to the rarity of this tumor type, the genetic and molecular characterization of SCL remains to be further elucidated. Recent research efforts, however, have shed light on potential sources of genetic alteration in SCL patients which may be conducive to engineering new cancer drugs. Table 3 summarizes various genetic profiling studies in literature that have identified genetic markers in SCL patients (Table 3). Next generation sequencing analysis of a panel of 26 genes was performed on 49 surgical specimens and has evaluated the prognostic impact and survival implications of the genetic profiles. The findings demonstrated that mutations in KRAS alone or in combination with the tumor protein p53 gene were associated with a decreased survival probability and a higher local and distant recurrence rate [7]. Along the same lines, Mehrad et al. concluded that KRAS mutation is predictive of outcome in SCL patients and is associated significantly with poor

survival [24].

Table 3: Common Genetic Markers Associated with SCL.

Study (Author, Year)	No. of Patients	% of Patients with Mutations
Schrock et al., 2017 [45]	125	TP53: 74%, KRAS, 34%, MET: 13.6%, EGFR: 8.8%, BRAF: 7.2%, HER2: 1.6%, RET: 0.8%
Li et al., 2017 [46]	7	TP53: 57.1%, MET: 14.1%, APC: 14.1%, HGF: 14.1%, PIK3CA: 14.1%, EGFR: 14.1%, BRAF: 14.1%
Lococo et al., 2016 [7]	49	TP53: 55%, KRAS: 39%, PIK3CA: 12%, STK11: 8%, APC: 6%, PTEN: 6%, BRAF: 2%. EGFR: 2%
Fallet et al., 2015 [47]	81	KRAS: 27.2%, EGFR: 22.2%, TP53: 22.2%, STK11: 7.4%, NOTCH1: 4.9%, NRAS: 4.9%, PI3KCA: 4.9%
Kaira et al., 2015 [48]	17	EGFR: 18%
Cancer Genome Atlas Research Network, 2014 [49]	230	TP53: 46%, KRAS: 33%, STK11: 17%, BRAF: 10%, PIK3CA: 7%, MET: 7%
Chang et al., 2011 [27]	42	TP53: 28.6%, EGFR: 23.8%
Italiano et al., 2009 [50]	22	KRAS: 38%, EGFR: 0%

Not only do these studies help implicate prognosis of SCL patients, but also convey information that aids in the potential creation of gene regulation drugs. EGFR tyrosine kinase inhibitors, which are commonly used to treat head and neck and lung cancers, have been show to induce a response in approximately 70% of NSCLCs with EGFR mutations [25-27]. However, as seen by the genetic profiling studies, only a small percentage of SCL patients possess the EGFR mutation.

Recent studies have alluded to a potential biomarker-driven target approach for SCL patients in the inhibition of MET-driven oncogenic pathways [24, 28, 29]. The specific alteration of the pathway features a mutation in which exon 14 of the MET gene is spliced. Liu et al. reports 8 (22%) cases of MET mutations leading to exon 14 skipping [28]. In the same study, dramatic response to crizotinib, a small-molecule kinase inhibitor for MET, was seen in a patient with chemotherapy-refractory disease possessing a MET exon 14 skipping mutation [28, 30].

Programmed death-ligand 1 (PD-L1) also provides a promising avenue of immunotherapeutic treatment in SCL patients. In 2013, Velcheti et al. demonstrated a high level of expression of PD-L1 in this disease, approximating 69% of SCL patients that were positive for PD-L1, which is higher than conventional expression in NSCLC patients [31]. Thus, the results from Velcheti et al. provide a rationale for increased emphasis of PD-L1 as a potential immunotherapeutic target. Despite its potential in creating new targeted immunotherapeutic drugs, higher levels of PD-L1 have also been shown to be a worse prognostic factor in SCL patients [32]. However, in light of its correlation to a poorer prognosis, PD-L1 remains to be a target in creating novel immunotherapy strategies in a disease that has otherwise been difficult to treat due to its rarity, aggressiveness, and occult nature.

Conclusion

This case illustrates the atypical nature of GI metastases in SCL, warranting physicians to proceed with caution in underestimating the burden of disease when patients diagnosed with SCL present with GI symptoms. In addition to gastrointestinal deposits, it has been reported in literature the copious amount of locations that SCL may metastasize to, ranging from the spine to upper lip. Because of a lack of response to chemotherapy, understanding the true burden of disease in SCL should be further emphasized as surgical intervention remains the standard of care. Although efforts have produced promising avenues to treatment, more research needs to be conducted to understand sarcomatoid carcinoma of the lung, which has otherwise been difficult to treat due to its rarity, aggressiveness, and occult nature.

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Disclosures

None.

References

1. Ro JY, Chen JL, Lee JS, Sahin AA, Ordóñez NG et al. (1992) Sarcomatoid carcinoma of the lung. Immunohistochemical and ultrastructural studies of 14 cases. *Cancer* 69: 376-386. [Crossref]
2. Braham E, Ben Rejeb H, Aouadi S, Kilani T, El Mezni (2014) Pulmonary carcinosarcoma with heterologous component: report of two cases with literature review. *Ann Transl Med* 2: 41. [Crossref]
3. Yendamuri S, Caty L, Pine M, Adem S, Bogner P et al. (2012) Outcomes of sarcomatoid carcinoma of the lung: a Surveillance, Epidemiology, and End Results Database analysis. *Surgery* 152: 397-402. [Crossref]
4. Chen CH, Chen WM, Tung SY, Wu CS, Tong WL et al. (2015) Gastrointestinal metastasis from primary sarcomatoid carcinoma of the lung: a case report and review of the literature. *World J Surg Oncol* 13: 174. [Crossref]

5. Martin LW, Correa AM, Ordonez NG, Roth JA, Swisher SG et al. (2007) Sarcomatoid carcinoma of the lung: a predictor of poor prognosis. *Ann Thorac Surg* 84: 973-980. [Crossref]
6. Nakajima M, Kasai T, Hashimoto H, Iwata Y, Manabe H et al. (1999) Sarcomatoid carcinoma of the lung: a clinicopathologic study of 37 cases. *Cancer* 86: 608-616. [Crossref]
7. Lococo F, Gandolfi G, Rossi G, Pinto C, Rapicetta C et al. (2016) Deep Sequencing Analysis Reveals That KRAS Mutation Is a Marker of Poor Prognosis in Patients with Pulmonary Sarcomatoid Carcinoma. *J Thorac Oncol* 11: 1282-1292. [Crossref]
8. Ouziane I, Saber Boutayeb, Hind Mrabti, Issam Lalya, Mouna Rimani et al. (2014) Sarcomatoid carcinoma of the lung: a model of resistance of chemotherapy. *N Am J Med Sci* 6: 342-345. [Crossref]
9. Yang CJ, Hwang JJ, Kang WY, Chong IW, Wang TH et al. (2006) Gastro-intestinal metastasis of primary lung carcinoma: clinical presentations and outcome. *Lung Cancer* 54: 319-323. [Crossref]
10. Berger A, Cellier C, Daniel C, Kron C, Riquet M et al. (1999) Small bowel metastases from primary carcinoma of the lung: clinical findings and outcome. *Am J Gastroenterol* 94: 1884-1887. [Crossref]
11. Jung SP, Han KM, Bae JW, Kim JH (2014) Recurrent intussusception caused by intestinal metastasis of pulmonary pleomorphic carcinoma. *Kaohsiung J Med Sci* 30: 378-379. [Crossref]
12. McNeill PM, Wagman LD, Neifeld JP (1987) Small bowel metastases from primary carcinoma of the lung. *Cancer* 59: 1486-1489. [Crossref]
13. Huang SY, Shen SJ, Li XY (2013) Pulmonary sarcomatoid carcinoma: a clinicopathologic study and prognostic analysis of 51 cases. *World J Surg Oncol* 11: 252. [Crossref]
14. Travis WD (2010) Sarcomatoid Neoplasms of the Lung and Pleura. *Arch Pathol Lab Med* 134: 1645-1658. [Crossref]
15. Beasley MB, Brambilla E, Travis WD (2005) The 2004 World Health Organization classification of lung tumors. *Semin Roentgenol* 40: 90-97. [Crossref]
16. Lin MW, Wu CT, Chang YL (2014) Intussusception Caused by Intestinal Metastasis from Lung Pleomorphic Carcinoma. *Ann Thorac Cardiovasc Surg* 20: 635-638. [Crossref]
17. Karim NA, Schuster J, Eldessouki I, Gaber O, Namad T et al. (2017) Pulmonary sarcomatoid carcinoma: University of Cincinnati experience. *Oncotarget* 9: 4102-4108. [Crossref]
18. Lin Y, Yang H, Cai Q, Wang D, Rao H et al. (2016) Characteristics and Prognostic Analysis of 69 Patients with Pulmonary Sarcomatoid Carcinoma. *Am J Clin Oncol* 39: 215-222. [Crossref]
19. Shum E, Stuart M, Borczuk A, Wang F, Cheng H et al. (2016) Recent advances in the management of pulmonary sarcomatoid carcinoma. *Expert Rev Respir Med* 10: 407-416. [Crossref]
20. Lococo F, Rapicetta C, Cardillo G, Stefani A, Margaritora S et al. (2017) Pathologic Findings and Long-Term Results After Surgical Treatment for Pulmonary Sarcomatoid Tumors: A Multicenter Analysis. *Ann Thorac Surg* 103: 1142-1150. [Crossref]
21. Gu L, Xu Y, Chen Z, Pan Y, Lu S (2015) Clinical analysis of 95 cases of pulmonary sarcomatoid carcinoma. *Biomed Pharmacother* 76: 134-140. [Crossref]
22. Chaft JE, Sima CS, Ginsberg MS, Huang J, Kris MG et al. (2012) Clinical outcomes with perioperative chemotherapy in sarcomatoid carcinomas of the lung. *J Thorac Oncol* 7: 1400-1405. [Crossref]
23. Vieira T, Girard N, Ung M, Monnet I, Cazes A et al. (2013) Efficacy of First-Line Chemotherapy in Patients with Advanced Lung Sarcomatoid Carcinoma. *J Thorac Oncol* 8: 1574-1577. [Crossref]
24. Mehrad M, Roy S, LaFramboise WA, Petrosko P, Miller C et al. (2018) KRAS mutation is predictive of outcome in patients with pulmonary sarcomatoid carcinoma. *Histopathology* 73: 207-214. [Crossref]
25. Harari PM (2004) Epidermal growth factor receptor inhibition strategies in oncology. *Endocr Relat Cancer* 11: 689-708. [Crossref]
26. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I et al. (2010) Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 11: 121-128. [Crossref]
27. Chang YL, Wu CT, Shih JY, Lee YC (2011) EGFR and p53 Status of Pulmonary Pleomorphic Carcinoma: Implications for EGFR Tyrosine Kinase Inhibitors Therapy of an Aggressive Lung Malignancy. *Ann Surg Oncol* 18: 2952-2960. [Crossref]
28. Liu X, Jia Y, Stoopler MB, Shen Y, Cheng H et al. (2016) Next-Generation Sequencing of Pulmonary Sarcomatoid Carcinoma Reveals High Frequency of Actionable MET Gene Mutations. *J Clin Oncol* 34: 794-802. [Crossref]
29. Lee C, Usenko D, Frampton GM, McMahon C, Ali SM et al. (2015) MET 14 Deletion in Sarcomatoid Non-Small-Cell Lung Cancer Detected by Next-Generation Sequencing and Successfully Treated with a MET Inhibitor. *J Thorac Oncol* 10: e113-e114. [Crossref]
30. Ayoub NM, Al-Shami KM, Alqudah MA, Mhaidat NM (2017) Crizotinib, a MET inhibitor, inhibits growth, migration, and invasion of breast cancer cells in vitro and synergizes with chemotherapeutic agents. *Onco Targets Ther* 10: 4869-4883. [Crossref]
31. Velcheti V, Rimm DL, Schalper KA (2013) Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1). *J Thorac Oncol* 8: 803-805. [Crossref]
32. Yvorel V, Patoir A, Casteillo F, Tissot C, Fournel P et al. (2017) PD-L1 expression in pleomorphic, spindle cell and giant cell carcinoma of the lung is related to TTF-1, p40 expression and might indicate a worse prognosis. *PLoS One* 12: e0180346. [Crossref]
33. Arshad HS, Dudekula RA, Niazi M, Malik S, Khaja M et al. (2017) A Rare Case of Sarcomatoid Carcinoma of the Lung with Spine Metastasis, Including a Literature Review. *Am J Case Rep* 18: 760-765. [Crossref]
34. Takeda K, Matsushita H, Kubozono M, Tanabe T, Ishikawa Y et al. (2016) Definitive Chemoradiotherapy for Advanced Pulmonary Sarcomatoid Carcinoma. *Int Med* 55: 3325-3330. [Crossref]
35. Le T, Mayer M, Sailors J, Gerber DE, Truelson JM (2017) Upper lip metastasis of sarcomatoid carcinoma of the lung - an unusual site of disease: a case report. *J Med Case Rep* 11: 18. [Crossref]
36. Romano A, Grassia M, Rossetti AR, Esposito G, Braccio B et al. (2015) Sarcomatoid Carcinoma of the lung: A rare case of three small intestinal intussusceptions and literature review. *Int J Surg Case Rep* 13: 48-50. [Crossref]
37. Oliveira MF, Watanabe SC, Andrade MP, Rotta JM, Pinto FC et al. (2013) Sarcomatoid carcinoma of the lung with brain metastases. *J Bras Pneumol* 39: 753-756. [Crossref]
38. Weissferdt A, Kalhor N, Correa AM, Moran CA (2017) "Sarcomatoid" carcinomas of the lung: a clinicopathological study of 86 cases with a new perspective on tumor classification. *Hum Pathol* 63: 14-26. [Crossref]
39. Roesel C, Terjung S, Weinreich G, Hager T, Chalvatzoulis E et al. (2017) Sarcomatoid carcinoma of the lung: a rare histological subtype of non-small cell lung cancer with a poor prognosis even at earlier

tumour stages. *Interact Cardiovasc Thorac Surg* 24: 407-413. [Crossref]

40. Steuer CE, Behera M, Liu Y, Fu C, Gillespie TW et al. (2017) Pulmonary Sarcomatoid Carcinoma: An Analysis of the National Cancer Data Base. *Clin Lung Cancer* 18: 286-292. [Crossref]
41. Lococo F, Cardillo G, Stefani A, Margaritora S et al. (2017) Pathologic Findings and Long-Term Results After Surgical Treatment for Pulmonary Sarcomatoid Tumors: A Multicenter Analysis. *Ann Thorac Surg* 103: 1142-1150. [Crossref]
42. Gu L, Xu Y, Chen Z, Pan Y, Lu S (2015) Clinical analysis of 95 cases of pulmonary sarcomatoid carcinoma. *Biomed Pharmacother* 76: 134-140. [Crossref]
43. Mochizuki T, Ishii G, Nagai K, Yoshida J, Nishimura M et al. (2008) Pleomorphic carcinoma of the lung: clinicopathologic characteristics of 70 cases. *Am J Surg Pathol* 32: 1727-1735. [Crossref]
44. Venissac N, Pop D, Lassalle S, Berthier F, Hofman P et al. (2007) Sarcomatoid lung cancer (spindle/giant cells): an aggressive disease? *J Thorac Cardiovasc Surg* 134: 619-623. [Crossref]
45. Schrock AB, Li SD, Frampton GM, Suh J, Braun E et al. (2017) Pulmonary Sarcomatoid Carcinomas Commonly Harbor Either Potentially Targetable Genomic Alterations or High Tumor Mutational Burden as Observed by Comprehensive Genomic Profiling. *J Thorac Oncol* 12: 932-942. [Crossref]
46. Li X (2017) Clinical Significance and Next-Generation Sequencing of Chinese Pulmonary Sarcomatoid Carcinoma. *Scientific Rep* 7: 3947.
47. Fallet V, Saffroy R, Girard N, Mazieres J, Lantuejoul S et al. (2015) High-throughput somatic mutation profiling in pulmonary sarcomatoid carcinomas using the LungCarta™ Panel: exploring therapeutic targets. *Ann Oncol* 26: 1748-1753. [Crossref]
48. Kaira K, Horie Y, Ayabe E, Murakami H, Takahashi T et al. (2010) Pulmonary Pleomorphic Carcinoma: A Clinicopathological Study Including EGFR Mutation Analysis. *J Thorac Oncol* 5: 460-465. [Crossref]
49. The Cancer Genome Atlas Research Network (2014) Comprehensive molecular profiling of lung adenocarcinoma. *Nature* 511: 543-550. [Crossref]
50. Italiano A, Cortot AB, Ilie M, Martel-Planche G, Fabas T et al. (2009) EGFR and KRAS status of primary sarcomatoid carcinomas of the lung: Implications for anti-EGFR treatment of a rare lung malignancy. *Int J Cancer* 125: 2479-2482. [Crossref]