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A Case Report of a Rare Sarcomatoid Poorly Differentiated Adenocarcinoma Harboring Concurrent Mutations in the ROS1, EGFR, ARID1A, and NFKBIA Genes in the Lung

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Abstract

ROS1 and EGFR are primary oncogenic drivers in non-small cell lung cancer (NSCLC) pathogenesis. However, EGFR mutations and ROS1 fusions are generally mutually exclusive in NSCLC, leading to a negligible probability of their co-occurrence. Consequently, clinical data and treatment strategies for their simultaneous presence are remarkably scarce. This report details the first recorded case of a sarcomatoid, poorly differentiated lung adenocarcinoma harboring both a ROS1 fusion and an EGFR mutation, alongside ARID1A and NFKBIA gene mutations. Moreover, this case study encompasses a review of instances featuring concurrent ROS1 and EGFR mutations. The identified genetic alterations in ROS1, EGFR, ARID1A, and NFKBIA are pivotal in the etiology of NSCLC. These mutations significantly influence disease progression and are essential for the development of personalized therapeutic approaches. Recognizing the unique genetic profiles in patients permits healthcare providers to devise customized treatment regimens that target these specific mutations, thereby enhancing patient outcomes in NSCLC.

Keywords

Non-Small Cell Lung Cancer, ROS1, EGFR, Sarcomatoid

1. Case Information

The 64-year-old female patient, with no smoking history, was admitted to the hospital in June 2020 due to a persistent cough and hemoptysis lasting over 10

days. A pulmonary computed tomography (CT) scan (Figure 1) revealed a 4.2 cm × 4.0 cm × 1.9 cm mass in the basal segment of the right lung's lower lobe. The mass exhibited lobulation and spiculation, along with partial bronchial stenosis and obstruction, and displayed mild enhancement in the contrast-enhanced scan. Blood tests identified no significant abnormalities, except for an elevated level of cytokeratin 19 fragment (CYFRA21-1), which was 4.53 ng/ml.

The patient underwent a thoracoscopic dissection of the right lower lobe and the hilar and mediastinal lymph nodes. The definitive pathological diagnosis was poorly differentiated adenocarcinoma of the sarcomatoid, solid subtype, featuring interstitial infiltration by lymphoplasmacytic cells, eosinophils, and neutrophils. Additionally, numerous foam cells and areas of patchy necrosis were observed, and there was suspected pleural invasion. There was no evidence of intravascular tumor thrombus or nerve invasion. Metastases were detected in lymph node groups 7 (5 nodes), 9 (1 node), 10 (2 nodes), and 11 (2 nodes). Immunohistochemical staining yielded the following results: Pan-CK (+), Vimentin (+), CD4 (diffuse +), CD68 (histiocyte +), CD38 (partial +), CD8 (partial +), Alk (D5F3) (−), CEA (+), CK7 (+), Napsin A (−), TTF-1 (partial +), CD3 (partial +), CD30 (−), PD-L1 (TPS > 80%), and a Ki-67 index of approximately 30%. The tumor was staged as pT2N2M0, IIIa. Postoperative tissue samples were analyzed via polymerase chain reaction (PCR) and indicated ROS1 fusion. Furthermore, next-generation sequencing (NGS) (Table 1 and Figure 2) revealed an SLC34A2-ROS1 fusion, concurrently with mutations in the EGFR, ARID1A, and NFKBIA genes.

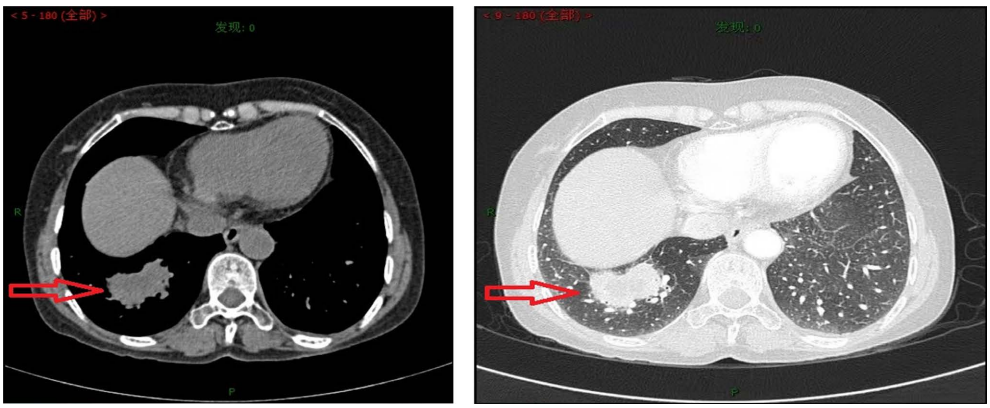

Figure 1. Shows a space-occupying lesion in the basal segment of the lower lobe of the right lung, as indicated by the arrow.

Table 1. NGS test results.

Genes	Transcript	Variation region	Changes of nucleotides and amino acids	Mutation type	Mutation frequency/ copy number
SLC34A2-ROS1	-	-	-	Fusion	5.8%
ARIDIA	NM_006015.4	Exon l	c.941G > T (p.G314V)	Missense	49.01%
EGFR	NM_005228.3	Exon 28	c.3584C > G (p.A1195G)	Missense	47.72%
NFKBIA	NM_020529.2	Exon 1	c.123G > C (p.E41D)	Missense	45.65%

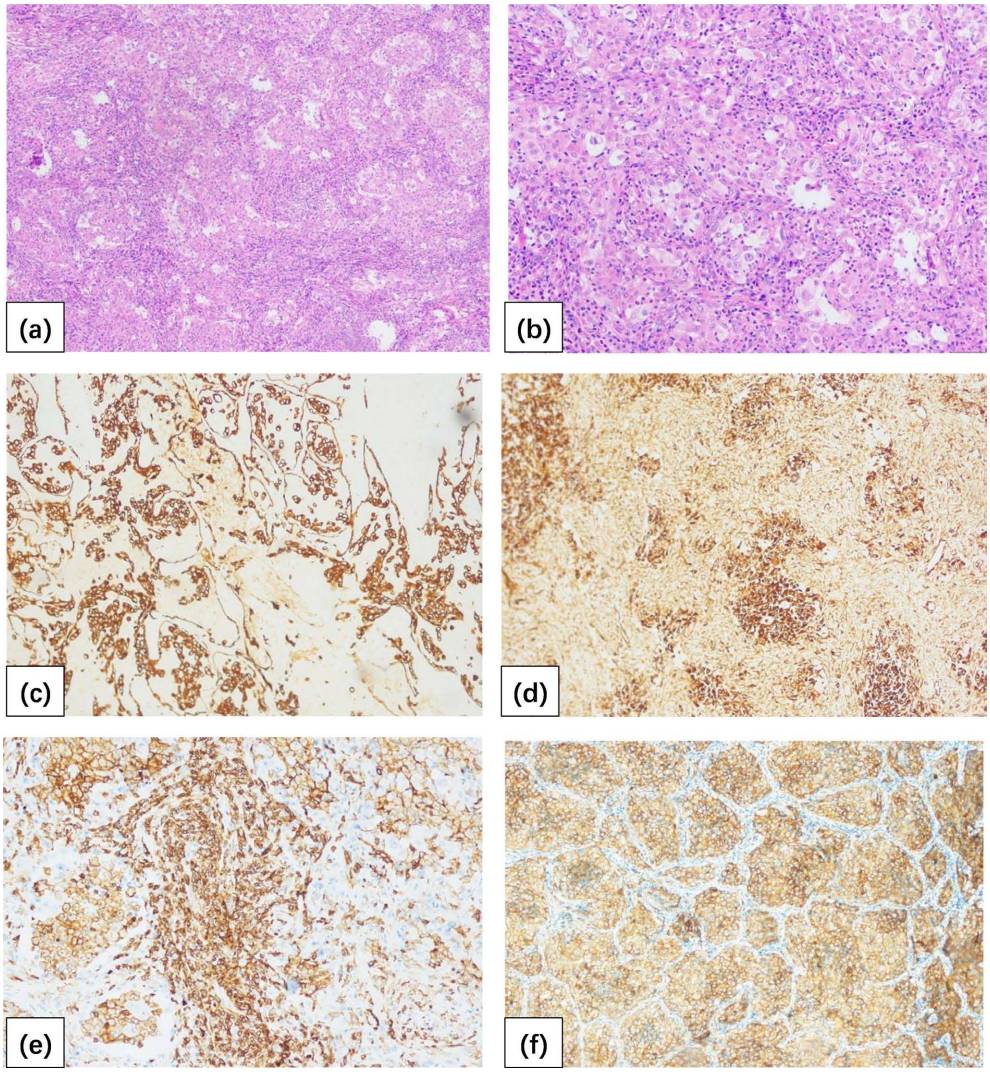

Figure 2. The hematoxylin–eosin and immunohistochemical staining results. (a) The hematoxylin and eosin staining (×100); (b) The hematoxylin and eosin staining (×200); (c) CK Immunohistochemical staining (×100); (d) Vimentin Immunohistochemical staining (×100); (e) ROS1 Immunohistochemical staining (×100); (g) PD-L1 Immunohistochemical staining (×100).

2. Treatment Course

In June 2020, the patient underwent thoracoscopic dissection of the right lower lobe and the hilar and mediastinal lymph nodes. Postoperative adjuvant chemotherapy was administered over five cycles, spanning from August to November 2020. The treatment regimen was as follows: in August 2020, the patient received 650 mg of pemetrexed monotherapy; in September, a combination of 650 mg pemetrexed and 40 mg carboplatin was administered from day 1 to day 4 for the second chemotherapy cycle. This was followed by three cycles of 650 mg pemetrexed plus 10 mg loplatin from day 1 to day 4 in October, November, and December 2020, respectively. Following the completion of five chemotherapy cycles, a course of radiotherapy began in January 2021. The treatment involved administering a total radiation dose of 5000 cGy over 25 fractions (PTV 5000

cGy/25F). TKIs was not used during the whole treatment.

3. Follow-Up and Outcome

The patient experienced prominent improvement in symptoms and a significant therapeutic response following the postoperative adjuvant radiotherapy and chemotherapy, as evidenced by a reduction in cytokeratin 19 fragment (CYFRA21-1) levels to the normal range of 2.24 ng/ml. Throughout a three-year follow-up period, no recurrence was observed and the patient's condition remained stable. Multiple CT scans during this period revealed postoperative alterations in the right lower lung without evidence of new or recurrent lesions.

4. Discussion

The ROS1 proto-oncogene, also known as c-Ros sarcoma oncogene receptor tyrosine kinase (ROS1), is infrequently found in non-small cell lung cancer (NSCLC), representing only 1% - 2% of cases. Located on chromosome 6q22, ROS1 spans 7368 bp and comprises 43 exons. A variety of ROS1 fusion partner genes have been identified, with CD74 being the most prevalent. These fusion proteins exhibit distinct subcellular localizations and activate specific signaling pathways, fostering tumor cell proliferation. Typically, ROS1 gene fusions are more common among younger female patients, non-smokers, and those with lung adenocarcinoma (LUAD) subtype [1] [2] [3].

Tyrosine kinase inhibitors (TKIs) targeting ROS1 fusions include crizotinib, ceritinib, lorlatinib, and entrectinib. Crizotinib, the first FDA-approved first-line treatment for advanced ROS1-rearranged NSCLC, has demonstrated an overall response rate of 72% (95%CI, 58-84%) and a median overall survival of 51.4 months [4] (**Table 2**).

The epidermal growth factor receptor (EGFR), also known as HER1 or ERBB1, is situated on chromosome 7p12 and encodes a transmembrane receptor protein. It is one of the most frequently mutated genes in lung cancer, with the majority of EGFR mutations occurring within exons 18 - 21 of the tyrosine kinase domain. EGFR TKIs are the most efficacious treatment for EGFR-mutated NSCLC. Evidence suggests that EGFR mutations and ROS1 fusions are typically mutually exclusive, with cases harboring both being exceedingly rare and presenting primary resistance to EGFR TKIs [5] [6] [7] [8]. A review of the literature revealed nine cases of concurrent ROS1 fusion and EGFR mutation, all of which involved non-smokers with adenocarcinoma histopathology. Among these, two displayed sarcomatoid differentiation, yet no recurrences were observed post-adjuvant chemotherapy and follow-up. In the three cases reported by Mao, EGFR-TKI treatment was ineffective; however, two responded to crizotinib, with an average progression-free survival (PFS) of 10.6 months. This response did not impact overall survival (OS). Chen's two cases exhibited a transient response to gefitinib, indicating the need for further investigation into the efficacy of EGFR-TKIs in patients with both ROS1 fusion and EGFR co-mutation.

Table 2. Clinical characteristics and prognostic evaluation of patients with ROS1 and EGFR co-mutations.

Case	Author	Gender	Age Smoking (years)	History	Histology	TNM staging	Mutated genes	Treatment	Response	PFS (month)	Os (month)
1	Chen, *et al.*	NA	NA	No	Adenocarcinoma	NA	RO51 EGFR (19del)	Gefitinib	PR	NA	NA
2	Chen, *et al.*	NA	NA	No	Adenocarcinoma	NA	RO51 EGFR(19del)	Gefitinib	PR	NA	NA
3	Chen, *et al.*	NA	NA	No	Adenocarcinoma	NA	ROS1 EGFR(19del)	NA	NA	NA	NA
4	Chen, *et al.*	NA	NA	No	Adenocarcinoma	NA	ROS1 EGFR (20-ins)	NA	NA	NA	NA
5	Mao, *et al.*	Female	55	No	Adenocarcinoma	NA	CD74-ROS1 EGFR(19del)	Crizotinib	5D	7.0	15.4
6	Mao, *et al.*	Male	45	No	Adenocarcinoma	NA	EZR-ROS1 EGFR (19del)	Crizatinib	PR	23.0	35
7	Mao, *et al.*	Male	59	No	Adenocarcinoma	NA	CD74-ROS1 EGFR (L858R)	Crizatinib	PD	2.0	24
8	Zhu, *et al.*	Female	50	No	Adenocarcinoma with sarcomatoid differentiation	T2aNOMO stage Ib	CD74-ROS1 EGFR(L858R)	Postoperative chemotherapy	RO resectiona	NA	NA
9	present case	Female	64	No	Adenocarcinoma with sarcomatoid differentiation	T2N2MO stage IIIa	SLC34A2-ROS1 EGFR ARIDIA NFKBIA	Postoperative chemotherapy and radiotherapy	RO resectiona	NA	NA

Abbreviations: PFS (progression-free survival), OS (overall survival), PR (partial response), SD (stable disease), PD (progressive disease), NA (not available), R0 (Complete resection with no microscopic residual tumor).

Immunotherapy with immune checkpoint inhibitors (ICIs) has not been explored in these cases, leaving the potential effectiveness of ICIs unknown in these cases [9] [10] [11].

ARID1A, a tumor suppressor gene and the most commonly mutated component of the SWI/SNF complex, is frequently altered in diverse human malignancies, including lung cancer. Downregulation of ARID1A correlates with advanced TNM stage and poor NSCLC prognosis [12] [13]. Moreover, EGFR mutations are detectable in 9 to 22 percent of ARID1A-mutated tumors. EGFR-TKI treatment yields suboptimal results in NSCLC with concurrent ARID1A and EGFR mutations, resulting in shorter PFS. Inverse associations have been observed between ARID1A mutations and EGFR co-mutated NSCLC with immune cell infiltration and immune checkpoint scores. ARID1A-mutated NSCLC patients treated with ICIs have a median OS of 21 months, compared to just 10 months for those with wild-type genes, suggesting that immunotherapy may be more beneficial for ARID1A-mutated NSCLC [13].

In glioblastoma, deletions of NFKBIA and amplifications of EGFR are mutually exclusive; however, their relationship in NSCLC is yet to be elucidated. This case presents concurrent alterations, indicating a potential interplay. The

miR-224/QKI-5/miR-196b-5p/NFKBIA signaling pathway has been identified as playing a role in the progression of NSCLC. Targeting this pathway could potentially provide therapeutic benefits for NSCLC patients with NFKBIA mutations [14] [15] [16].

Both the present case and the case reported by Zhu showed adenocarcinoma sarcomatoid pathological changes, suggesting that EGFR mutation and ROS1 fusion may lead to sarcomatoid changes in pathophysiology. In addition, ARID1A mutation may also be one of the causes of sarcomatoid transformation [17].

5. Brief Summary

We present an uncommon instance of lung cancer characterized by concurrent mutations in the EGFR gene and ROS1 fusion. The exceptional outcomes observed following surgical intervention and adjunctive postoperative chemotherapy suggest that patients with this specific genetic profile may exhibit heightened sensitivity to chemotherapeutic regimens. Additionally, the prognostic implications of dense CD4+ T lymphocyte infiltration in the tumor vicinity and pronounced PD-L1 expression, as detected by immunohistochemistry, warrant further exploration. The efficacy of immunotherapy for this subgroup of patients remains an area for future investigation.

Although targeted therapies for ROS1 and EGFR mutations exist, the complex interplay between multiple genetic alterations must be factored into therapeutic decision-making. Crafting personalized treatment strategies for NSCLC patients harboring both ROS1 fusion and EGFR mutations is of paramount importance. Concurrently, elucidating the contributions and expressions of other genetic players, such as ARID1A and NFKBIA, is crucial in enhancing the precision and effectiveness of therapeutic interventions for NSCLC patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Shaw, A.T., Ou, S.-H.I., Bang, Y.-J., *et al.* (2014) Crizotinib in ROS1-Rearranged Non-Small-Cell Lung Cancer. *The New England Journal of Medicine*, **371**, 1963-1971. https://doi.org/10.1056/NEJMoa1406766

[2] Yu, Z.-Q., Wang, M., Zhou, W., *et al.* (2022) ROS1-Positive Non-Small Cell Lung Cancer (NSCLC): Biology, Diagnostics, Therapeutics and Resistance. *Journal of Drug Targeting*, **8**, 845-857. https://doi.org/10.1080/1061186X.2022.2085730

[3] Guaitoli, G., Bertolini, F., Bettelli, S., *et al.* (2021) Deepening the Knowledge of ROS1 Rearrangements in Non-Small Cell Lung Cancer: Diagnosis, Treatment, Resistance and Concomitant Alterations. *International Journal of Molecular Sciences*, **22**, Article 12867. https://doi.org/10.3390/ijms222312867

[4] Azelby, C.M., Sakamoto, M.R., Bowles, D.W., *et al.* (2021) ROS1 Targeted Therapies: Current Status. *Current Oncology Reports*, **23**, Article No. 94. https://doi.org/10.1007/s11912-021-01078-y

[5] Wang, D.D., Ma, L.C., Wong, M.P., *et al.* (2015) Contribution of EGFR and ErbB-3 Heterodimerization to the EGFR Mutation-Induced Gefitinib and Erlotinib Resistance in Non-Small-Cell Lung Carcinoma Treatments. *PLOS ONE*, **10**, e0128360. https://doi.org/10.1371/journal.pone.0128360

[6] Noronha, V., Choughule, A., Patil, V.M., *et al.* (2017) Epidermal Growth Factor Receptor Exon 20 Mutation in Lung Cancer: Types, Incidence, Clinical Features and Impact on Treatment. *OncoTargets and Therapy*, **10**, 2903-2908. https://doi.org/10.2147/OTT.S133245

[7] Wu, S.-G. and Shih, J.-Y. (2018) Management of Acquired Resistance to EGFR TKI-Targeted Therapy in Advanced Non-Small Cell Lung Cancer. *Molecular Cancer*, **17**, Article No. 38. https://doi.org/10.1186/s12943-018-0777-1

[8] Xu, Y.Y., Chang, H., Wu, L.J., *et al.* (2020) High Prevalence of ROS1 Gene Rearrangement Detected by FISH in EGFR and ALK Negative Lung Adenocarcinoma. *Experimental and Molecular Pathology*, **117**, Article 104548. https://doi.org/10.1016/j.yexmp.2020.104548

[9] Zhu, Y.-C., Xu, C.-W., Ye, X.-Q., *et al.* (2016) Lung Cancer with Concurrent EGFR Mutation and ROS1 Rearrangement: A Case Report and Review of the Literature. *OncoTargets and Therapy*, **9**, 4301-4305. https://doi.org/10.2147/OTT.S109415

[10] Mao, Y.J. and Wu, S.X. (2017) ALK and ROS1 Concurrent with EGFR Mutation in Patients with Lung Adenocarcinoma. *OncoTargets and Therapy*, **10**, 3399-3404. https://doi.org/10.2147/OTT.S133349

[11] Wu, S.F., Wang, J.H., Zhou, L.J., *et al.* (2015) Clinicopathological Characteristics and Outcomes of ROS1-Rearranged Patients with Lung Adenocarcinoma without EGFR, KRAS Mutations and ALK Rearrangements. *Thoracic Cancer*, **6**, 413-420. https://doi.org/10.1111/1759-7714.12191

[12] Wang, T., Guo, J.Y., Liu, W.H., *et al.* (2020) Downregulation of ARID1A Is Correlated with Poor Prognosis in Non-Small Cell Lung Cancer. *Translational Cancer Research*, **9**, 4896-4905. https://doi.org/10.21037/tcr-20-2263

[13] Jin, F.K., Yang, Z.G., Shao, J.B., *et al.* (2023) ARID1A Mutations in Lung Cancer: Biology, Prognostic Role, and Therapeutic Implications. *Trends in Molecular Medicine*, **29**, 646-658. https://doi.org/10.1016/j.molmed.2023.04.005

[14] Furukawa, M., Soh, J., Yamamoto, H., *et al.* (2013) Silenced Expression of NFKBIA in lung Adenocarcinoma Patients with a Never-Smoking History. *Acta Medica Okayama*, **67**, 19-24.

[15] Bredel, M., Scholtens, D.M., Yadav, A.K., *et al.* (2011) NFKBIA Deletion in Glioblastomas. *The New England Journal of Medicine*, **364**, 627-637. https://doi.org/10.1056/NEJMoa1006312

[16] Zhu, W.Y., Yu, Y., Ye, Y.X., *et al.* (2023) MiR-196b-5p Activates NF-κB Signaling in Non-Small Cell Lung Cancer by Directly Targeting NFKBIA. *Translational Oncology*, **37**, Article 101755. https://doi.org/10.1016/j.tranon.2023.101755

[17] Liang, X.H., Li, Q., Xu, B., *et al.* (2019) Mutation Landscape and Tumor Mutation Burden Analysis of Chinese Patients with Pulmonary Sarcomatoid Carcinomas. *International Journal of Clinical Oncology*, **24**, 1061-1068. https://doi.org/10.1007/s10147-019-01454-6