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CASE REPORT

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Disseminated intravascular coagulation complicating diagnosis of *ROS1*-mutant non-small cell lung cancer: A case report and literature review

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Abstract

Disseminated intravascular coagulation (DIC) is a rare paraneoplastic complication in advanced solid malignancies, with success of treatment and survival dependent on treatment of the underlying malignancy. Best estimates suggest an incidence of 1.6–6.8% in cancer, with risk factors being advanced disease, older age, and adenocarcinoma, especially of lung origin. Few cases, however, have reported on an association between DIC and oncogene-addicted lung cancers, especially those containing ROS proto-oncogene 1 (*ROS1*) mutations, however precedent exists to suggest increased prothrombotic rates in tumors harboring this mutation. We present a young woman with *ROS1*-mutant non-small-cell lung cancer who presented in DIC and subsequently developed complications of both hemorrhage and thrombosis. Following initiation of targeted treatment, rapid resolution of laboratory coagulation derangement was observed and clinical improvement quickly followed. This event underscores the need for rapid evaluation of lung molecular panels and the dramatic resolution of life-threatening illness that can occur with institution of appropriate therapy. This case contributes to growing evidence for a possible underlying link between oncogene addicted tumors and abnormalities of coagulation.

KEYWORDS

disseminated intravascular coagulation, non-small-cell lung cancer, oncogene addiction, paraneoplastic syndrome, ROS1 mutation

INTRODUCTION

DIC (disseminated intravascular coagulopathy) is a clinicopathological syndrome characterized by consumptive coagulopathy without localization. One manifestation is as decompensated DIC, presenting with both bleeding and thrombosis with a predilection for microvasculature, but in solid malignancies such clinical presentations are often indolent and highly variable, depending on the efficacy of compensatory mechanisms and the intensity of the underlying malignancy.[1–3] Few cases have reported on an association between DIC and oncogene-addicted lung cancers. In this report, we present a young woman with *ROS1*-mutant non-small-cell lung cancer who presented in DIC with excellent response to initiation of targeted treatment.

CASE PRESENTATION

A 54-year-old female ex-light-smoker with no significant comorbidities presented to the emergency department in February 2021 with symptoms of lethargy, headaches, and

myalgias for 2 weeks. Outpatient imaging on the day of presentation with a CT chest, abdomen, and pelvis displayed stigmata of diffuse metastatic disease with innumerable pulmonary, intracranial, hepatic, and sclerotic osseous lesions (Figure 1(a)).

Thorough physical examination was unremarkable. She was febrile on admission and pathology results noted an elevated bilirubin at 25 μmol/L, moderately deranged liver enzymes in a cholestatic pattern, and mildly abnormal coagulation profile with international normalized ratio (INR) 1.6 IU, activated partial thromboplastin time (APTT) 40.5 s, and prothrombin time (PT) 21.4 s. Platelet count was 258×10^9/L. She was commenced on IV vitamin K in the context of liver dysfunction and lung biopsy confirmed primary lung adenocarcinoma. Shortly after biopsy she developed a moderate perilesional hematoma at the site of biopsy and a small hemothorax (Figure 1(b)), requiring intubation and respiratory support. She improved with supportive measures and was extubated after 24 h. Worsening coagulation derangement was noted, hematology was consulted, and the diagnosis of diffuse intravascular coagulopathy (DIC) was confirmed.

She was commenced on intensive blood product support, eventually comprising 9 units of packed red blood cells, 70 units of cryoprecipitate, and 6 units of fresh frozen plasma, aiming for a fibrinogen level >1.5 g/L, with discussions commenced about emergent administration of chemotherapy with carboplatin and pemetrexed at day 9 of her admission. During this time emergency radiation was also administered (12Gy/2#) for both intracranial and pulmonary lesions due to persistent hemoptysis with dosing selected to avoid overlap with her anticipated systemic therapy.

Shortly after her first cycle of chemotherapy, immunohistochemistry (IHC) on her biopsy sample showed strong diffuse staining for ROS proto-oncogene 1 (ROS1) protein (SP384 antibody). Epidermal growth factor receptor (*EGFR*) testing and anaplastic lymphoma kinase (*ALK*) IHC were negative. Fluorescence in situ hybridization (FISH) confirmed a *ROS1* rearrangement (Figure S1), and the decision was made to switch treatment to entrectinib.

Prior to this, she suffered a further desaturation event with cyanosis, chest pain, and tightness. CT pulmonary angiography confirmed bilateral segmental and subsegmental pulmonary emboli with imaging evidence of right heart strain, and she again required intensive care admission for respiratory support, heparin infusion, and ongoing management of DIC (Figure 1(c)).

Following institutional approval, entrectinib was commenced 23 days after diagnosis. Dramatic laboratory improvement of DIC followed within 3 days with no further blood product requirements (Figures S2 and S3). She was discharged 7 days later.

At subsequent outpatient follow-up she remained well with no further evidence of DIC and near normalization of liver function. Initial progress imaging after 6 weeks noted a partial response, and she continues on entrectinib with good tolerance.

DISCUSSION

DIC is a rare complication of advanced malignancy, with the best estimation of incidence as 6.8% from one large cohort study. This study noted the diagnosis to be most common in adenocarcinomas of lung, breast, prostate, colorectal, and pancreatic origin.[4] Multivariate analysis in this cohort also suggested an increased risk for older patients, male gender, advanced malignancies, and presence of necrosis in the tumor specimen.[4] In contrast to this, Kanaji et al. assessed 716 patients with pathologically proven lung cancer and reported a prevalence of DIC of only 0.7% overall and 1.5% in stage IV disease.[5]

Besides these studies, reports are otherwise limited to isolated cases, and despite the low prevalence suggested by Kanaji et al., non-small-cell lung cancers (NSCLC) predominate. Most of these cases pre-date widespread use of methods to detect molecular fusions and therefore whether an association exists between oncogene driver mutations and DIC is uncertain. The few cases in which an oncogene driver was demonstrated are given in Table 1. Of note,

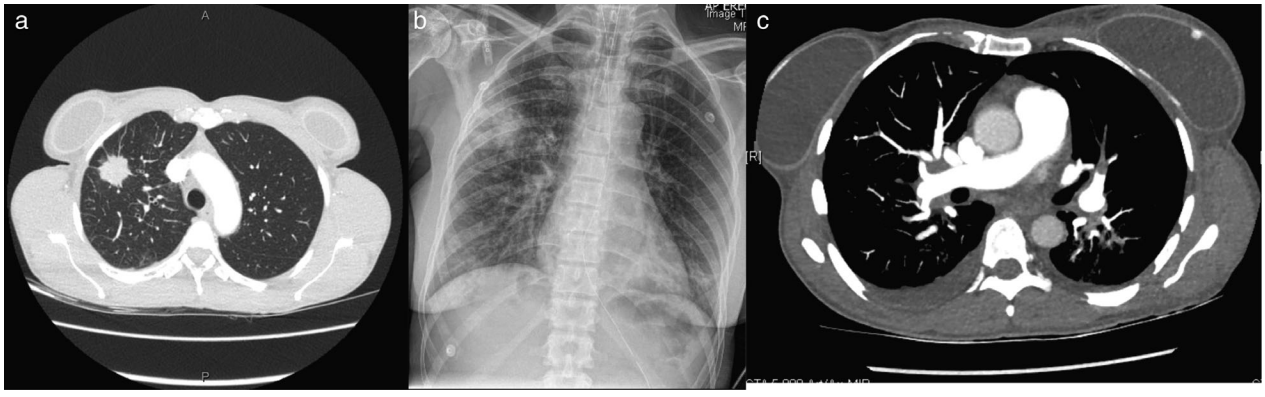

FIGURE 1 (a) Axial view from computed tomography of chest displaying primary lung lesion. (b) Plain film x-ray of perilesional hematoma with associated haemothorax. (c) Computed tomography axial view of segmental pulmonary emboli

TABLE 1 Table of reported cases of disseminated intravascular coagulation in lung cancers with driver mutations

Author	Year	Study	Number	Mutation	Stage	Comment
Brosseau et al.[15]	2018	Case report	1	ROS1	IV	Complete response to crizotinib
Kim et al.[16]	2018	Case report	1	EGFR	IV	
Fujita et al.[17]	2021	Case report	1	EGFR ALK	IV	L858R Treated successfully with osimertinib
Toyokawa et al.[18]	2013	Case report	1	ALK	IV	
De Giglio et al.[19]	2017	Case report	1	ALK	IV	Died before treatment institution
Tanaka et al.[20]	2016	Case report	1	ALK	IV	Rapid response to alectinib

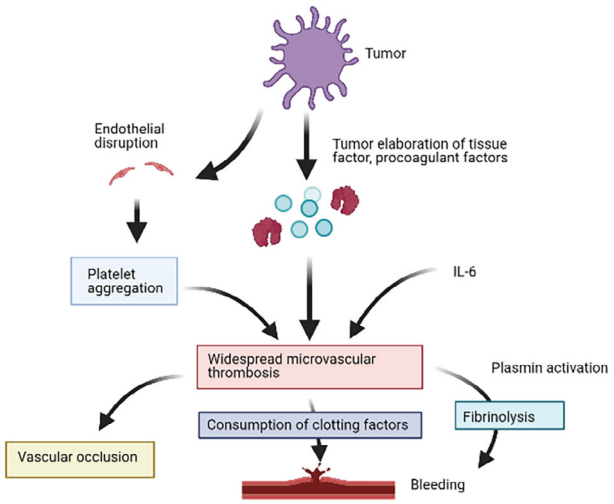

FIGURE 2 Suggested mechanism of action of tumor-mediated disseminated intravascular coagulation

however, *ROS1*-rearranged NSCLCs have been associated with a higher incidence of venous thromboembolism. Recent analysis from the METROS trial noted a 3–5-fold higher incidence of venous thromboembolism in *ROS1*-rearranged NSCLC compared to *ROS1* wild-type NSCLCs.[6]

In the setting of malignancy, DIC is posited to result from endothelial disruption compounded by tumor elaboration of procoagulant molecules, such as tissue factor (TF) and cancer procoagulant, driven by pro-inflammatory cytokines, especially interleukin-6.[7,8] This results in platelet aggregation with widespread microvascular thrombosis, consumption of coagulation factors, and generation of fibrin degradation products due to compensatory fibrinolysis (Figure 2). Success of DIC treatment therefore revolves around treatment of the underlying malignant process,[1] confirmed in this case with dramatic resolution of requirements for blood products and no further thrombotic or hemorrhagic events following commencement of entrectinib. This event underscores the importance of rapid evaluation of molecular panels in the setting of newly diagnosed metastatic lung cancer. Initial treatment with carboplatin and pemetrexed was rationalized in the context of a life-threatening hemorrhagic event, although following *ROS1* positivity treatment was swiftly changed due to greater proven efficacy with targeted treatments compared to chemotherapy.[9]

ROS1 fusions occur in roughly 1–2% of NSCLC, typically in adenocarcinomas in light or nonsmokers. These are oncogenic drivers with constitutive tyrosine kinase activity activating cell survival and growth signaling pathways, including *MAPK/ERK*, *JAK/STAT*, and *PI3K/AKT* cascades.[10] There is considerable partner gene heterogeneity with the most common *ROS1* fusion in NSCLC being *CD74-ROS1*, which is also associated with a higher incidence of intracranial metastases.[11] *ROS1* fusions are druggable targets in NSCLC, with a number of effective therapeutics.[12] Entrectinib is a multitargeted tyrosine kinase inhibitor of *ROS1* fusions, as well as Tropomyosin receptor kinase (*TRK*) *A/B/C* fusions and *ALK*, specifically designed for blood–brain barrier penetrance, making it the preferred choice of treatment in this case.[13] Reported objective response rates in patients with intracranial disease exceed 70%, with a duration of response over 12 months.[13] For this patient ongoing follow-up will be required to monitor closely for toxicities and early signs of disease progression.

In conclusion, this report describes a rare case of widespread de novo metastatic *ROS1*-fusion positive lung cancer with an initial presentation of DIC causing numerous complications, which promptly resolved following commencement of targeted therapy. However, despite high initial responses, resistance to targeted treatments is common, and it remains uncertain whether DIC could re-manifest as a sign of development of resistance.[14]

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

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REFERENCES

1. Levi M, ten Cate H. Disseminated intravascular coagulation. N Engl J Med. 1999;341:586–92.

2. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86: 1327–30.
3. Adelborg K, Larsen JB, Hvas AM. Disseminated intravascular coagulation: epidemiology, biomarkers, and management. Br J Haematol. 2021;192:803–18.
4. Sallah S, Wan JY, Nguyen NP, Hanrahan LR, Sigounas G. Disseminated intravascular coagulation in solid tumors: clinical and pathologic study. Thromb Haemost. 2001;86:828–33.
5. Kanaji N, Mizoguchi H, Inoue T, Tadokoro A, Watanabe N, Ishii T, et al. Clinical features of patients with lung cancer accompanied by thromboembolism or disseminated intravascular coagulation. Ther Clin Risk Manag. 2018;14:1361–8.
6. Chiari R, Ricciuti B, Landi L, Morelli AM, Delmonte A, Spitaleri G, et al. ROS1-rearranged non–small-cell lung cancer is associated with a high rate of venous thromboembolism: analysis from a phase II, prospective, multicenter, two-arms trial (METROS). Clin Lung Cancer. 2020;21:15–20.
7. Sato T, Tsujino I, Ikeda D, Ieko M, Nishimura M. Trousseau's syndrome associated with tissue factor produced by pulmonary adenocarcinoma. Thorax. 2006;61:1009–10.
8. Levi M. Clinical characteristics of disseminated intravascular coagulation in patients with solid and hematological cancers. Thromb Res. 2018;164:S77–81.
9. Gridelli C, De Marinis F, Di Maio M, Cortinovis D, Cappuzzo F, Mok T. Gefitinib as first-line treatment for patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutation: review of the evidence. Lung Cancer. 2011;71: 249–57.
10. D'Angelo A, Sobhani N, Chapman R, Bagby S, Bortoletti C, Traversini M, et al. Focus on ROS1-positive non-small cell lung cancer (NSCLC): crizotinib, resistance mechanisms and the newer generation of targeted therapies. Cancer. 2020;12:3293.
11. Drilon A, Jenkins C, Iyer S, Schoenfeld A, Keddy C, Davare MA. ROS1-dependent cancers – biology, diagnostics and therapeutics. Nat Rev Clin Oncol. 2021;18:35–55.
12. Solomon BJ, Loong HHF, Summers YJ, Thomas ZM, French PP, Lin BK, et al. Correlation between overall response rate and progression-free survival/overall survival in comparative trials involving targeted therapies in molecularly enriched populations. J Clin Oncol. 2020;38(15 Suppl):3588.
13. Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21: 261–70.
14. Voulgaris E, Pentheroudakis G, Vassou A, Pavlidis N. Disseminated intravascular coagulation (DIC) and non-small cell lung cancer (NSCLC): report of a case and review of the literature. Lung Cancer. 2009;64:247–9.
15. Brosseau S, Gounant V, Naltet C, Théou-Anton N, Cazes A, Smonig R, et al. Lazarus syndrome with crizotinib in a non-small cell lung cancer patient with ROS1 rearrangement and disseminated intravascular coagulation. Clin Lung Cancer. 2018;19:e57–61.
16. Kim JS, Ryu JS, Jeon SH, Kim HJ, Nam HS, Cho JH, et al. Dramatic response of acute disseminated intravascular coagulation to erlotinib in a patient with lung adenocarcinoma with activating EGFR mutation. J Int Med Res. 2018;46:533–7.
17. Fujita K, Naka M, Ito T, Kanai O, Maekawa K, Nakatani K, et al. Successful management of a lung cancer patient harbouring both EGFR mutation and EML4-ALK fusion gene with disseminated intravascular coagulation. Respir Med Case Rep. 2021;33:101393.
18. Toyokawa G, Takenoyama M, Watanabe S, Toyozawa R, Inamasu E, Kojo M, et al. Dramatic response to crizotinib in an ALK-positive adenocarcinoma patient with disseminated intravascular coagulation. J Thorac Oncol. 2013;8:e96–8.
19. De Giglio A, Porreca R, Brambilla M, Metro G, Prosperi E, Bellezza G, et al. Fatal acute disseminated intravascular coagulation as presentation of advanced *ALK*−positive non-small cell lung cancer: does oncogene addiction matter? Thromb Res. 2018;163:51–3.
20. Tanaka H, Taima K, Morimoto T, Nakamura K, Tanaka Y, Itoga M, et al. Dramatic response to alectinib in a patient of ALK-rearranged lung cancer with poor performance status. BMC Res Notes [Internet]. 2016; 9:173. http://europepmc.org/abstract/MED/26987388; https://doi.org/10.1186/s13104-016-1983-9; https://europepmc.org/articles/PMC4794901; https://europepmc.org/articles/PMC4794901?pdf=render.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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