Case Report

A Case of Metastatic Renal Cell Carcinoma Presenting with Acute Disseminated Intravascular Coagulation

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ABSTRACT

Disseminated intravascular coagulation (DIC) is a clinic pathological syndrome characterized by bleeding, thrombosis, or both, which are laboratory signs of coagulation and activation of fibrinolytic systems. This study focused on a case of acutely presenting DIC, which is a very rare complication of renal cell carcinoma (RCC). The patient was a 48-year-old male admitted to the emergency room due to shortness of breath and hemoptysis in the last couple of days. Computed Tomography scans indicated bilateral pulmonary nodules (metastasis), hypodense thrombus in the left pulmonary artery branch, thrombus in the right atrium and right ventricle, solid lesion (RCC?) in the right kidney lower pole. The patient was diagnosed with acute DIC with clinical and laboratory findings. Supportive therapy was initiated, a transbronchial biopsy was performed from the pleural lesion, and the patient was diagnosed with RCC. Pazopanib 400 mg (1x2) was prescribed. The patient responded quickly to the treatment and was clinically relieved. In the second month of treatment, the patient died from massive hemoptysis due to DIC. Acute DIC occurrence due to solid tumors is rare, but has a very poor prognosis. The treatment of underlying disease for DIC is the most effective approach in cancer patients. In the literature there is only one case of RCC-related acute DIC, who had a very short survival time as our case had.

Keywords: *Disseminated Intravascular Coagulation, Clear Cell Renal Cell Carcinoma, Pazopanib, Therapy, Cardiac Thrombus.*

ÖZ

Akut Dissemine İntravasküler Koagülasyon ile Başvuran Metastatik Renal Hücreli Karsinom Olgusu

Dissemine intravasküler koagülasyon (DİK), pıhtılaşma ve fibrinolitik sistemlerin aktivasyonunun laboratuvar bulguları olan kanama, tromboz veya her ikisi ile karakterize klinikopatolojik bir sendromdur. Bu vaka, renal hücreli karsinomun (RHK) çok nadir bir komplikasyonu olan, akut olarak ortaya çıkan bir DİK olgusuna odaklanmıştır. Son birkaç gündür nefes darlığı ve hemoptizi nedeniyle acil servise başvuran 48 yaşında bir erkek hastanın çekilen Bilgisayarlı Tomografisinde bilateral pulmoner nodüller (metastaz), sol pulmoner arter dalında hipodens trombüs, sağ atriyum ve sağ ventrikülde trombüs, sağ böbrek alt polünde solid lezyon (RHK?) tespit edildi. Hastaya klinik ve laboratuvar bulguları ile akut DİK tanısı konuldu. Destek tedavisi başlandı, plevral lezyondan transbronşiyal biyopsi alındı ve hastaya RHK tanısı konuldu. Pazopanib 400 mg (1x2) reçete edildi. Hasta tedaviye hızlı yanıt verdi ve klinik olarak rahatladı. Tedavinin ikinci ayında hasta DİK'e bağlı masif hemoptiziden öldü. Solid tümörlerden kaynaklanan akut DİK nadirdir, ancak çok kötü prognoza sahiptir. DİK için altta yatan hastalığın tedavisi kanser hastalarında en etkili yaklaşımdır. Literatürde de bizim olgumuz gibi çok kısa sağ kalım süresi olan sadece bir RHK'ye bağlı akut DİK olgusu bulunmaktadır.

Anahtar Sözcükler: *Dissemine Intravasküler Koagülasyon, Berrak Hücreli Renal Hücreli Karsinom, Pazopanib, Tedavi, Kardiyak Trombüs.*

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Disseminated intravascular coagulation (DIC) is a dynamic pathological process triggered by abnormal activation of the blood coagulation pathway (1). DIC is a clinic pathological syndrome characterized by bleeding, thrombosis, or both, which are laboratory signs of coagulation and activation of fibrinolytic systems (2). Most cancer patients present with a chronic or low-grade DIC phenotype, where procoagulant factors are slowly released and compensated. However, when blood is exposed to a large number of procoagulants in a short period of time, acute DIC may develop, resulting in bleeding, thromboembolic events, or even death (3). Research shows that the incidence of DIC is 6.8% in malignant solid tumors. The type of DIC-related dominant tumors is adenocarcinoma, which generally originate from the gastrointestinal tract (frequently signet ring cell type), pancreas, lung, breast or prostate (4). There are two reported cases of DIC-related dominant tumors developing secondary to renal cell cancer (RCC). The first case was admitted for subacute DIC, from which he eventually died (5). The second one was a metastatic RCC case with chronic DIC (6). We described a case of acute DIC, which is a very rare complication of RCC.

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CASE REPORT

A 48-year-old male patient with no known chronic disease history had shortness of breath for the last couple of days. He was admitted to our emergency department due to the increase in dyspnea and complaints of hemoptysis. Computed Tomography (CT) scans indicated bilateral pulmonary nodules (metastasis), bilateral pleural thickening, the largest of which being on the upper lobe of the left lung (6x5 cm) and causing rib destruction, hypodense thrombus in the left pulmonary artery branch, thrombus in the right ventricle (5x3.7 cm in diameter) and right atrium (2.5x1.5 cm in diameter), solid lesion (RCC?) in the right kidney lower pole (61x55x57 mm), and multiple paraaortic lymph nodes (Figure 1A, 1B, 2).

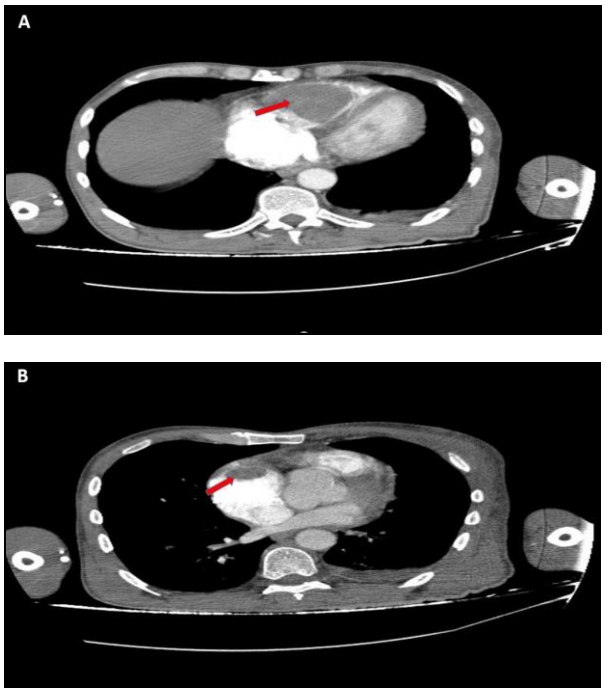

Figure 1A, B. *Axial Thoracic Imaging by Computed Tomography Imaging at Diagnosis.* ***A****, Right Ventricle Thrombus (Red Arrow).* ***B****, Right Atrial Thrombus (Red Arrow).*

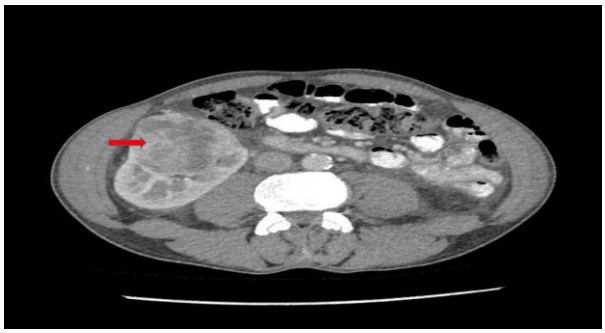

Figure 2. *Axial Abdominal Imaging by Computed Tomography Imaging at Diagnosis, Exophytic Right Renal Mass (Red Arrow).*

He was hospitalized to establish a final diagnosis and treatment. Anticoagulant therapy was recommended for pulmonary embolism and cardiac thrombus in the consultation of cardiology and chest diseases. He had an initial white blood cell (WBC) of 13,800 /uL, hemoglobin (Hgb) of 8 g/dl (from 11.1 to 17.1), platelet count of $34x10^3$/uL (150-400), reticulocyte count of $185.9x10^9$ /L (40-70), fibrinogen of 267.38 mg/dl, international normalized ratio (INR) of 1.22, prothrombin time (PT) of 15.2 sec (from 10 to 14), activated partial thromboplastin time (aPTT) of 32 sec, D-dimer of >7.5 mg/L (0-0.55), and LDH of 1443 u/L (120-246) (Table 1).

Table 1. *Laboratory findings and blood drawn at admission.*

	Value	Reference
WBC count (10^3/µl)	13.800	3800 - 8600
Hgb (g/dl)	8	11.1 - 17.1
Platelets (uL)	34 x 10^3	150 - 400
Reticulocyte (L)	185.9 x 10^9	40 - 70
Fibrinogen (mg/dl)	267.38	180 - 350
INR	1.22	
PT (sec)	15.2	10 - 14
aPTT (sec)	32	21 - 36
D-dimer (mg/L)	>7.5	0 - 0.55
LDH (u/L)	1443	120 - 246

WBC; White Blood Cell, Hgb; Hemoglobin, INR; İnternational Normalized Ratio, PT; Prothrombin Time, aPTT; Activated Partial Thromboplastin Time, LDH; Lactate Dehydrogenase.

He consulted with the hematology department to assess for potential DIC. Clinical and physical examination showed low procalcitonin and no signs of active inflammation. Therefore, the possibility of infection was ruled out. Schistocytes and thrombocytopenia were observed in the peripheral smear. He had a score of 6 on the International Society on Thrombosis and Hemostasis (ISTH) diagnostic scoring system for DIC, and therefore, was diagnosed with DIC due to malignancy (7). Treatment targeted at the underlying disease or plasmapheresis was recommended. In the follow-up, the patient whose platelet count values were between $20\text{-}29x10^3$/uL was recommended by the hematology, instead of plasmapheresis, underlying disease treatment, when platelet count was between $30\text{-}50x10^3$, enoxaparin sodium subcutaneous 0.6 ml 1x1, platelet count >50 x 10^3/uL, enoxaparin sodium 2x1 and platelet suspension support. However, no renal biopsy was performed because the patient had low platelet count. Instead, transbronchial biopsy was performed on the pleural lesion in the lung because he had a low risk of bleeding. In the meantime, platelet suspension was administered, and occasional hemoptysis and nosebleed were observed. During the 14-day hospitalization, the patient was administered 14 units of pooled platelet suspension and four units of apheresis platelet suspension. Fatigue and weight loss were observed in the patient during follow-up. He was pathologically diagnosed with RCC on August 29, 2019, and therefore, started to receive Pazopanib 400 mg (1x2). He had platelet count greater than $50x10^3$ for the first time after on September 1, 2019 and received anticoagulants twice a day without transfusion. He had an almost complete regression of hemoptysis. He had an Hgb of 11 and platelet count of $107x10^3$/uL on September 18, 2019. The hematology department assessed his perip-

heral smear. The clinical presentation, regression of thrombocytopenia, and absence of schistocytes showed that he had somewhat improved DIC. He had less shortness of breath and was prescribed enoxaparin sodium 0.6 ml (1x1) and pazopanib 400 mg (1x2) and then discharged. Two weeks later, he visited our department complaining of fatigue and weakness. He had an Hgb of 10.6 and platelet count of 103 x 10^3/uL. He had had normal liver and kidney function values, and therefore, continued receiving the same treatment. He was readmitted to the emergency outpatient clinic two days after his last visit due to the worsening of hemoptysis and shortness of breath. He was hospitalized again. His platelet count dropped (platelet: 29x10^3/uL) and coagulation parameters worsened (PT:18 sec, INR:1.51). He was followed up in the intensive care unit for two days and died from massive hemoptysis and respiratory failure.

DISCUSSION

Renal cell carcinoma (RCC) is a heterogeneous group of cancer resulting from renal tubular epithelial cells and is one of the top ten cancers worldwide (8). RCC is the most common type of renal tumor, which is about five percent of all cancers in men and three percent in women, with an increased incidence in the last decade (9). According to the Surveillance Epidemiology and End Results (SEER; the United States) database, the mean age of RCC patients is 64 years, and has almost a normal distribution. If someone younger than 46 years of age (lowest decimal of the age distribution) is diagnosed with RCC, the possibility of an underlying hereditary kidney cancer syndrome should be taken into account as it accounts for 3–5% of all RCCs (10). Most common metastasis in RCC occurs to the lung, retroperitoneum, bone, and brain, and to the liver to a lesser extent (11). We also observed lung metastasis in our patient.

For patients with surgically resectable RCC, the standard of care is partial or radical nephrectomy and surgical excision with a curative intent. However, patients with inoperable or metastatic RCC are systematically treated with target agents and/or immune control point inhibitors. RCC is very vascular, and therefore, sorafenib, sunitinib, pazopanib, axitinib, lenvatinib, and cabozantinib, which are tyrosine kinase inhibitors targeting the VEGF signaling axis, are used for first- and second-line metastatic RCC therapy (12-14). Agents targeting the mammalian target of rapamycin are used. Recent studies have focused on the combination of anti-VEGF therapy with new generation immune control point inhibitors, such as antibodies against the programmed cell death protein ligand 1 (PDL1) (avelumab and atezolizumab) and 1 (PD1) (nivolumab and pembrolizumab) (15). Another combination (Checkmate 214, NCT02231749) is nivolumab with ipilimumab, the latter of which is an inhibitor of the T cell control point cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (16). This combinations are recommended at the category 1 level of the first-line therapy for metastatic RCC patients, who are at middle and high-risk. Our patient was at high risk but could not receive that combination for treatment because his health insurance did not cover it. He received Pazopanib 800 mg in the first-line therapy and tolerated it without any side effects. At first, the therapy resulted in rapid clinical improvement, however, he died from severe tumor burden and DIC at the end of the second month of treatment. One RCC patient with low tumor burden received pazopanib treatment after three cycles of chemotherapy and then were followed up in the 11th month (6). However, another patient with severe clinical manifestation of RCC was receiving anticoagulant therapy but died four weeks after her admission before she started receiving treatment for the disease (5). According to a study on 1117 patients with solid tumors, those with overt DIC (9 months) had significantly lower survival rates than those with non-overt DIC (14 months) ($p = 0.005$). This indicates that serious complications, such as DIC, have a great impact on cancer outcomes (4).

Patients with cancer may sometimes present with venous thromboembolism or pulmonary embolism before the diagnosis of cancer. However, thrombotic complications of cancer are not limited to thrombosis but may manifest themselves with other signs of procoagulant state in its most fulminant form presenting as DIC (17). The clinical manifestation of DIC in cancer may be thrombosis, bleeding, or the combination of the two (1). Thrombotic microangiopathy may also occur (18). Our patient was also admitted to the clinic due to bleeding and thrombosis, which are signs of a severe procoagulant state. Laboratory findings are necessary to confirm a diagnosis. Acute DIC almost always presents with thrombocytopenia and microangiopathic hemolytic anemia.

The treatment of underlying disease for DIC is the most effective approach in cancer patients. However, supportive therapy has also been used in combination with targeted therapy to prevent rapid exacerbation of coagulopathy (17). Targeted therapy depends on the type of cancer. Some of the target therapies are cytotoxic chemotherapy, immunotherapy, molecularly targeted therapy, radiation therapy, endocrine therapy, and surgical therapy. Targeted therapy is the most important cancer treatment, and success in the treatment of primary disease results in withdrawal of DIC (19). As for anticoagulant therapy, chemotherapy combined with low molecular weight heparin reduces the mortality rate in patients with solid tumors (17). On the other hand, recombinant human soluble thrombomodulin (thrombomodulin alfa, TM-α) improves DIC scores and treats solid tumors, at least temporarily, and results in prolonged survival rate when the control of DIC and treatment of the underlying disease are compatible (20). Our patient also received transfusion support and low molecular weight heparin therapy until he received treatment for the disease.

Conclusion

Acute DIC from solid tumors is rare but a serious complication with a very poor prognosis. There is only one case of acute DIC from renal cell cancer. Similar to our case, that patient had a very short survival rate and was diagnosed with RCC after acute DIC had developed. Common DIC due to solid tumors is generally observed in patients with advanced tumors and is mostly diagnosed based on clinical and laboratory tests. Early diagnosis of overt DIC and initiation of systemic therapy is the key to the successful treatment of cancer-related DIC.

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