Severe digital ischemia coexists with thrombocytopenia in malignancy-associated antiphospholipid syndrome: A case report and review of literature

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Abstract

BACKGROUND
Paraneoplastic syndromes are characterized by atypical clinical manifestations. Several reports of hepatocellular carcinoma (HCC) paraneoplastic phenomena have been reported. They usually manifest as one type in an individual, but it is not common for the two clinical manifestations to occur simultaneously.

CASE SUMMARY
A 52-year-old female patient was admitted to hospital with pale skin and numbness of the second to fifth fingers in the left hand, which rapidly developed into severe digital ischemia. Computed tomography angiography revealed uneven thickness of the left ulnar artery with severe local luminal stenosis. Blood analysis during hospitalization showed persistent mild to medium thrombocytopenia and insensitive to hormonal therapy. Antiphospholipid antibody testing showed high titer of IgG anticardiolipin antibodies (aCLs), IgA aCLs, IgG anti-\(\beta_2\)-glycoprotein-I (anti-\(\beta_2\) GP) and IgA anti-\(\beta_2\) GP. The exact diagnosis was HCC when the high a-fetoprotein levels, computed tomography findings, and the history of chronic hepatitis B came together. This was a rare case of coexisting manifestations as presenting symptoms of malignancy-associated antiphospholipid syndrome. The patient underwent several operations, antithrombotic treatments and hormonal therapy. However, the patient refused chemotherapy and died 8 wk after diagnosis.

CONCLUSION
This report highlights the importance of atypical clinical changes that could alert the physicians to vigilance for a concomitant underlying malignancy.
Paraneoplastic syndromes, compared with cancer, are characterized by atypical clinical manifestations. This report described a case of hepatocellular carcinoma in which the presenting symptom was severe digital ischemia, mimicking Raynaud’s phenomenon, accompanied with thrombocytopenia, associated with antiphospholipid antibodies. This report highlights the importance of atypical clinical changes that could alert the physicians to be vigilant for concomitant underlying malignancy.

Case Presentation

Chief complaints
A 52-year-old female patient was admitted to hospital with pale skin and numbness of the left second to fifth fingers.

History of present illness
The patient’s symptoms started unprovoked about 1 d before when she rose in the morning. The left hand swelled quickly and showed a clear oblique blood supply boundary line (Figure 1A). Thus, the patient attended the emergency department.

History of past illness
The patient had no other medical history but was an asymptomatic carrier of hepatitis B virus for nearly 10 years. The patient had no history of hypertension or type 2 diabetes.

Personal and family history
The patient married at a young age and had two daughters as well as no history of vascular thrombosis and pregnancy morbidity.
Figure 1 Appearance of the patient’s hand during hospitalization. A: Pale skin of the second to fifth fingers in the left hand mimicking Raynaud’s phenomenon upon admission; B: The dorsal skin of the hand was necrotic and exfoliated in 1 wk, and dry gangrene occurred in the fingertips; C: The wound reached the standard for skin grafting about 3 wk after digital amputation; D: Appearance 1 wk after autologous skin grafting shows successful performance.

Physical examination
The patient’s vital signs were stable and oxygen saturation in room air was 99%, but left digital oxygen saturation was not detectable by the finger pulse oximeter. The skin temperature of the left second to fifth fingers decreased. The pulse of the left radial artery could be felt, but not that of the ulnar artery.

Laboratory examinations
Blood analysis during hospitalization showed a persistent mild to medium thrombocytopenia, with normal red blood cell and white blood cell. The changes in platelet count during hospitalization are presented in Figure 2. D-dimer was increased at 0.82 mg/L, with normal prothrombin time, international normalized ratio, fibrinogen, and activated partial thromboplastin time. Serum C-reactive protein was also normal and erythrocyte sedimentation rate was at 36 mm/h. Serological tests for human immunodeficiency virus and syphilis were negative. Serum complement and immunoglobulins were abnormal. aPL testing showed positive results: High titer (> 120 GPLU/mL) IgG anticardiolipin (aCL) antibodies, high titer (57 APLU/mL) IgA aCL, high titer (> 200 AU/mL) IgG anti-β2-glycoprotein-I (anti-β2 GPI), and high titer (90.10 AU/mL) IgA anti-β2 GPI. However, IgM aCL (4.24 MPLU/mL) and IgM anti-β2 GPI (2 AU/mL) were normal. Antinuclear antibody was also positive. However, lupus anticoagulant (LA) and Coombs’ test were negative. Serum carcinoembryonic antigen and CA 19-9 were within normal limits. However, serum a-fetoprotein level was dramatically increased to 1210 ng/mL. Electrocardiography and chest X-ray were normal. The laboratory values are shown in Table 1.

Imaging examinations
Arteriovenous color Doppler ultrasound of the upper extremity revealed that the blood flow signal of the proper digital artery was poor. The left upper brachial artery was further evaluated with computed tomography (CT) angiography. The latter revealed uneven thickness at the bifurcation of the left ulnar artery with severe local lumen stenosis, leading to slender branches, delayed imaging, and light imaging. It suggested that digital necrosis was mainly caused by a decrease in blood supply. Left hand X-ray showed no obvious bone destruction. On abdominal CT, dimensions of the liver were normal but contours were irregular. There were several mass lesions that appeared as mixed contrast in the arterial phase (Figure 3A) and lost their contrast in the portal venous phase (Figure 3B). Color Doppler ultrasound in the abdomen showed liver cirrhosis with multiple solid masses in the liver, and high enhancement in the arterial phase (Figure 3C).

FINAL DIAGNOSIS
The final diagnosis was HCC, left digital ischemia, thrombocytopenia, non-criteria antiphospholipid syndrome (APS), and chronic hepatitis B (old).
Table 1 Main laboratory values in the present case

| Item                                           | Laboratory value | Reference value |
|------------------------------------------------|------------------|-----------------|
| RBC \((10^{12}/L)\)                            | 3.68             | 3.8-5.1         |
| WBC \((10^{9}/L)\)                            | 6.81             | 3.5-9.5         |
| Platelet count \((10^{9}/L)\)                 | 41               | 150-450         |
| D-dimer (mg/L)                                 | 0.82             | < 0.55          |
| Prothrombin time (s)                           | 11.1             | 9.6-12.8        |
| Activated partial thromboplastin time (s)      | 28.2             | 24.8-33.8       |
| Fibrinogen (g/L)                               | 2.82             | 2.0-4.0         |
| International normalized ratio                 | 0.98             | 0.88-1.15       |
| Serum C-reactive protein (mg/L)                | 4.77             | < 5             |
| ESR (mm/h)                                     | 36               | < 38            |
| HIV                                           | Negative         | Negative        |
| HBV                                           | Positive         | Negative        |
| Syphilis                                      | Negative         | Negative        |
| Serum complement C3 (g/L)                      | 0.899            | 0.785-1.520     |
| Serum complement C4 (g/L)                      | 0.209            | 0.145-0.360     |
| IgG (g/L)                                      | 10.6             | 8.0-15.5        |
| IgA (mg/L)                                     | 950              | 836-2900        |
| IgM (mg/L)                                     | 1240             | 700-2200        |
| IgG anticardiolipin antibodies (GPLU/mL)       | > 120            | < 10            |
| IgA anticardiolipin antibodies (APLU/mL)        | 57               | < 10            |
| IgM anticardiolipin antibodies (MPLU/mL)        | 4.24             | < 10            |
| IgG anti-β2-γ2-glycoprotein-I (AU/mL)          | > 200            | < 20            |
| IgA anti-β2-γ2-glycoprotein-I (AU/mL)          | 90.1             | < 20            |
| IgM anti-β2-γ2-glycoprotein-I (AU/mL)          | 2                | < 20            |
| Antinuclear antibody                           | +1:100           | Negative        |
| Lupus anticoagulant                            | Negative         | Negative        |
| Coombs’ test                                   | Negative         | Negative        |
| Carcinoembryonic antigen (ng/mL)               | 1.87             | < 5             |
| α-fetoprotein                                  | > 1210           | < 7             |

RBC: Red blood cell; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus.

TREATMENT

The patient underwent three operations: emergency fasciotomy, elective finger amputation and skin grafting. Severe swelling of the hand leads to osteofascial syndrome, which can cause continuous deterioration of local capillary blood supply. Therefore, fasciotomy was performed upon admission to relieve the pressure within the fascial compartment. About 1 wk after admission, the proximal skin of the third to fifth fingers of the left hand were necrotic and exfoliated, and dry gangrene occurred in the fingertips (Figure 1B). Therefore, finger amputation was performed to completely remove the necrotic tissue (Figure 1C). Finally, after the wound was fresh and up to standard, the patient underwent autologous skin grafting (Figure 1D).

Intensified antithrombotic treatments with antiplatelets (aspirin 100 mg/d), and vascular microcirculation disorders improvement (papaverine hydrochloride 120 mg/d, cinzapide maleate 320 mg/d, alprostadil 2 mL/d), anticoagulants (low molecular weight heparin 4000 IU/d) and hormonal therapy (prednisone 30 mg/d)
Figure 2 The patient’s platelet count changed during hospitalization. The patient’s platelet count continued to decrease after admission, and gradually increased after hormonal therapy and platelet transfusion (1 U), but it did not reach the normal value (150-450 k/µL) during hospitalization.

Figure 3 Computed tomography and ultrasound imaging of the patient. A: Abdominal computed tomography showed normal dimensions of the liver but irregular contours. There were several mass lesions that took up mixed contrast in the arterial phase (white arrows); B: The mass lesions lost their contrast in the portal venous phase; C: Color Doppler ultrasound in the abdomen showed cirrhosis with multiple solid masses in the liver, and high enhancement in the arterial phase.

OUTCOME AND FOLLOW-UP
For anticoagulant therapy, heparin was replaced with rivaroxaban (10 mg/d) after discharge. In addition, the patient refused chemotherapy for HCC and died 8 wk after diagnosis.

DISCUSSION
Paraneoplastic phenomena may be the first sign of undiagnosed cancer, as in this case. Although the clinical manifestations of tumors and paraneoplastic syndromes are different, clinicians should realize that paraneoplastic phenomena are not caused by tumor mass effects or metastasis[2].

Paraneoplastic syndromes of HCC are not uncommon, and the incidence was reported to range from 20% to 31%[8,9]. Most reports indicate that paraneoplastic syndromes are associated with poor outcomes, but whether it is an independent prognostic factor for reduced HCC survival remains unclear[9,10]. The published case reports of paraneoplastic syndromes in HCC are summarized in Table 2. Although the reported cases of paraneoplastic syndromes are diverse, they can be grouped into six categories: Paraneoplastic hematologic syndrome, paraneoplastic rheumatologic syndrome, paraneoplastic dermatologic syndrome, paraneoplastic endocrine syndrome, paraneoplastic neurologic/neuropsychiatric syndrome, and paraneoplastic miscellaneous syndrome. In addition, the paraneoplastic syndromes usually appear before an HCC diagnosis. A study further found that erythrocytosis and hypercholesterolemia often developed earlier in the clinical course while hypoglycemia and hypercalcemia were usually terminal events[8]. In addition, most patients present one paraneoplastic syndrome and the occurrence of coexisting syndromes is uncommon.
To our knowledge, this was a rare case and the first report of HCC accompanied with paraneoplastic thrombocytopenia and severe digital ischemia, mimicking RP, as well as being associated with APS.

RP mainly involves bilateral fingers and mostly presents in young female patients. It is an episodic disease with short pallor phase, but not trophic changes and endothelial damage\cite{6}. However, severe, asymmetric RP that occurs after age 50 years may be a paraneoplastic phenomenon. RP has been found in various malignancies including lung cancer, renal cell carcinoma, and melanoma. In addition, > 80% of patients may progress to gangrene and ischemic necrosis\cite{11}.

### Table 2 Summary of reported paraneoplastic syndromes of hepatocellular carcinoma

| Category                        | Associated diseases/condition                                                                 | Ref.                  |
|---------------------------------|------------------------------------------------------------------------------------------------|-----------------------|
| **Hematologic syndromes**      | Severe eosinophilia                                                                            | Yuen et al\cite{23}, 1995 |
|                                 | Hemophagocytic syndrome                                                                       | Sakai et al\cite{24}, 2001 |
|                                 | Erythrocytosis                                                                                | Tsuchiya et al\cite{25}, 2009 |
|                                 | Leukemoid reaction                                                                            | Shin et al\cite{26}, 2011 |
|                                 | Thrombocytosis                                                                                | Abbas et al\cite{27}, 2019 |
| **Rheumatologic syndromes**    | Raynaud’s phenomenon                                                                         | Sahan et al\cite{6}, 2006 |
|                                 | Polymyositis                                                                                  | Thanapirom et al\cite{28}, 2014 |
|                                 | Dermatomyositis                                                                               | Chou et al\cite{7}, 2017 |
|                                 | Polyarthritis                                                                                 | Sathiyapalan et al\cite{29}, 2021 |
| **Dermatologic syndromes**     | Symptomatic porphyria                                                                         | Ochiai et al\cite{30}, 1997 |
|                                 | Disseminated superficial porokeratosis                                                          | Kono et al\cite{31}, 2000 |
|                                 | Cutaneous lupus erythematosus                                                                  | Ho et al\cite{32}, 2001 |
|                                 | Erythema nodosum                                                                              | Glinkov et al\cite{33}, 2003 |
|                                 | Pemphigus                                                                                     | Yokokura et al\cite{34}, 2006 |
|                                 | Generalized granuloma annulare                                                                  | Cho et al\cite{35}, 2018 |
| **Endocrine syndromes**        | Hypercholinesterasemia                                                                        | Tajiri et al\cite{36}, 1983 |
|                                 | Hyperlipidemia                                                                                | Makino et al\cite{37}, 1986 |
|                                 | Hyperestrogenia                                                                               | Salles et al\cite{38}, 1987 |
|                                 | Hyperthyroidism                                                                               | Carri et al\cite{39}, 1989 |
|                                 | Hyperthyroxinemia                                                                             | Nizam et al\cite{40}, 1995 |
|                                 | Carcinoid syndrome                                                                            | Nwokediuko et al\cite{41}, 2010 |
|                                 | Hypercalcaemia                                                                                | Newman et al\cite{5}, 2015 |
|                                 | Hyperglycemia                                                                                 | Kim et al\cite{42}, 2015 |
| **Neurologic or neuropsychiatric syndromes** | Necrotizing myopathy                                                                          | Misumi et al\cite{43}, 1988 |
|                                 | Neurologic manifestations                                                                      | Norris et al\cite{44}, 1997 |
|                                 | Demyelinating polineuropathy                                                                   | Walcher et al\cite{45}, 2002 |
|                                 | Peripheral neuropathy                                                                          | Matsui et al\cite{46}, 2015 |
|                                 | Neuropsychiatric manifestations                                                                 | Karam et al\cite{47}, 2020 |
|                                 | Hyperammonemic encephalopathy                                                                  | Lee et al\cite{48}, 2021 |
| **Miscellaneous syndromes**    | Hypertension                                                                                  | Arai et al\cite{4}, 1999 |
|                                 | Membranous glomerulonephritis                                                                  | Texier et al\cite{49}, 2004 |
|                                 | Nummular loss of the retinal pigment epithelium                                                | Lee et al\cite{50}, 2007 |
|                                 | Myasthenia gravis                                                                             | Vautravers et al\cite{51}, 2008 |
|                                 | Rhabdomyolysis                                                                                | Bárdos et al\cite{52}, 2021 |
In a French study, 15% of patients admitted for an initial occurrence of digital ischemia had an underlying cancer, including adenocarcinoma, squamous cell carcinoma, and lymphoid neoplasia[12]. However, the mechanism of paraneoplastic RP is still unknown, and its possible physiological mechanism includes a vasoconstrictive substance secreted by the tumor cells[13]. In the French study, it was suggested that paraneoplastic RP was mainly related to thrombocytosis[12]. However, this view contradicts the significant decrease in platelet count in our case, indicating the heterogeneous effects on the blood system (especially platelets) in different tumors. The etiology of thrombocytopenia can be categorized as problems of sequestration, decreased platelet production, increased platelet destruction, or increased platelet consumption. Corticosteroids can serve both therapeutic and diagnostic purposes, with positive response to these interventions lending support to an immune-mediated process[14]. In our case, the above view is also supported by the fact that the patient’s platelet count gradually recovered after oral prednisone treatment.

Based on the Sydney criteria, the core clinical manifestations of APS are arterial or venous thrombosis and obstetric complications and aPLs confirmed by laboratory detection[15]. Among them, the aPLs are defined as LA, aCL, and anti-β2GPI antibodies.

In addition, according to the Euro-Phospholipid Project, there are many common manifestations of APS, such as arthralgia (38.7%), immune thrombocytopenia (29.6%), arthritis (27.1%), migraine (20.2%), stroke (19.8%), but digital ischemia was rare, in only 3.3% of APS patients[16]. APS may be primary or related to a variety of diseases, such as systemic lupus erythematosus, Sjogren’s syndrome, infectious agents, and medication[17]. In particular, APS may be associated with various solid and hematological malignancies[18]. There are many case reports about aPLs antibodies related to malignant tumors, and their manifestations are also diverse. A Malaysian review has been fully summarized and reported[18]. However, the role and clinical significance of aPLs in the occurrence and development of malignant tumors are not clear. Since most cancer patients have thromboembolism, and aPLs are responsible for thrombus formation, it is speculated that aPLs may have a direct impact on thrombosis or contribute to the pathogenesis of cancer[18]. In addition, several mechanisms have been suggested to explain the association between aPLs and cancer including: (1) Production of autoantibodies as a response to tumor antigens; (2) Secretion of aCL antibodies from tumor cells; and (3) Production of monoclonal immunoglobulins with LA and aCL activities[19].

The relationship between RP and aPLs is also lacking, because vasospasm in small muscular arteries and finger arterioles rather than aPLs-mediated thrombosis is the underlying mechanism of the phenomenon[20].

Based on the APS criteria revision in the report of the 14th international congress on aPLs technical task force on APS clinical features[21], non-criteria manifestations of APS were considered as those suggested, recommended, or strongly recommended to be included. Thrombocytopenia is one of the major non-obstetric manifestations of APS, whereas RP is a minor one[22].

CONCLUSION

In elderly patients, the atypical clinical manifestations could alert the physicians to be vigilant for a concomitant underlying malignancy. The causality or interaction between cancer and paraneoplastic syndromes should be further studied.

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