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CASE REPORT

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A case of antiphospholipid antibody syndrome that manifested in the course of basal cell carcinoma

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Abstract A case of antiphospholipid antibody syndrome (APS) is presented, which manifested 5 years after onset of basal cell carcinoma (BCC). There were multiple collateral veins due to portal vein thrombosis. Because immunological abnormalities including anti-cardiolipin β_2 glycoprotein-I antibody improved after surgical resection of BCC, it is likely that APS had occurred as a paraneoplastic syndrome with BCC. This case suggests that it is necessary to investigate the presence of APS when BCC is complicated by some coagulopathies.

Key words Antiphospholipid antibody syndrome (APS) · Basal cell carcinoma (BCC) · Paraneoplastic · Portal · Thromboembolism

Introduction

Antiphospholipid antibody syndrome (APS) is characterized by repeated arterial or venous thrombosis, habitual miscarriage, serum antiphospholipid antibodies, or thrombocytopenia. Antiphospholipid antibody syndrome may occur as a primary disease, or secondary to systemic lupus erythematosus (SLE) or other autoimmune or infectious diseases. Recently, there have been many reports of APS occurring in patients with various neoplastic disorders[1]: lung cancer,[2,3] hematological malignancy,[4,5] ovarian cancer,[6] renal cell carcinoma,[7] and catastrophic APS, the most severe type of APS, which may occur in cases of malignancy.[8,9] Here, a rare case of APS that manifested 5 years after onset of basal cell carcinoma (BCC) and improved after its surgical resection is presented.

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Case report

A 64-year-old woman was referred to our hospital because of pancytopenia. She had been well until 5 years before when a small eruption occurred in the area between the eyebrows. Because there were no symptoms, she did nothing for the eruption even though it gradually enlarged. Five months before the initial examination, she felt exertional dyspnea and edema of the legs occurred. She was diagnosed as having chronic heart failure and given diuretics at another medical facility, and her symptoms subsided soon. Thirteen weeks before it was noted that she had pancytopenia and her serum anti-cardiolipin-β_2 glycoprotein-I antibody was positive (22.6 U/ml, normal <3.5 U/ml), and she was referred to our hospital for further examination. There was no history of thrombosis, abortion, or rheumatic diseases, nor family history of rheumatic diseases. On admission, there was a facial tumor measuring 11 × 7 mm in diameter in the area between the eyebrows (Fig. 1a), and telangiectasia on the anterior chest wall was found. The conjunctiva was anemic, and a mild systolic murmur was heard. The spleen was slightly palpable, and there were no varicose veins in the abdominal wall, or edema in the legs. On complete blood count, white blood cells were 1900/μl, hemoglobin 8.7 g/dl, and platelets 7.6×10^4/μl. Regarding blood chemistry, total protein 6.2 g/dl, albumin 3.2 g/dl, aspartate aminotransferase 26 IU/l, alanine aminotransferase 18 IU/l, lactate dehydrogenase 201 IU/l, total bilirubin 1.5 mg/dl, and haptoglobin was undetectable. On the coagulation test, prothrombin time (PT) was 15.8 s, activated partial thromboplastin time (APTT) was 42.4 s (control 32.0 s), lupus anticoagulant (LAC) determined by tissue thromboplastin inhibition test was 1.7 (normal <1.3), and protein C activity was 32% (normal >80%). Presence of LAC was confirmed by diluted Russell's viper venom time which showed 1.6-fold elongation of clotting time of patient's plasma as compared with that of normal plasma (normal <1.3-fold). On the immunological test, serum antinuclear antibody was negative, anti-cardiolipin-β_2 glycoprotein-I antibody titer was 25.1 U/ml, anti-cardiolipin IgG titer was

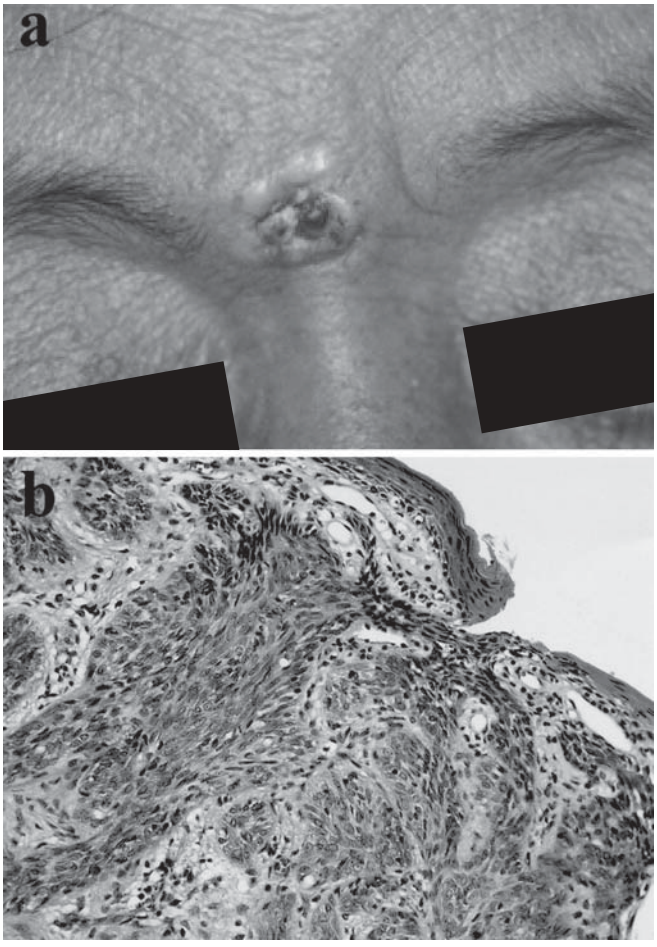

Fig. 1. **a** Facial tumor (11 × 7 mm in diameter) in the area between the eyebrows. **b** Pathological findings (H&E, ×200). Infiltration of round or spindle-shaped nucleated cells with an irregular focal structure and severe proliferation of connective tissue in the interstitium forming a morphea-like pattern are found

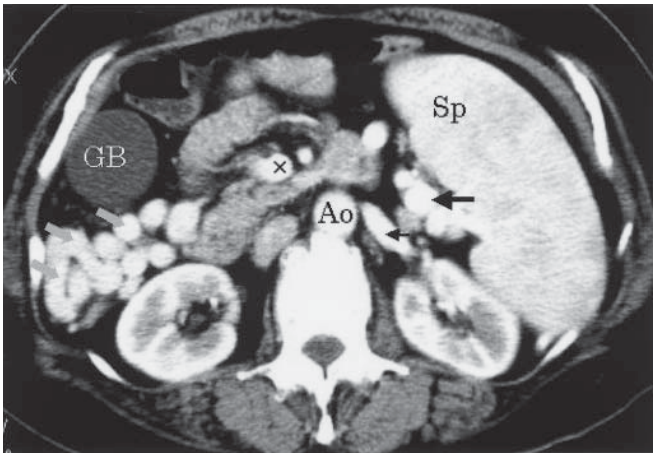

Fig. 2. Abdominal computed tomography scan enhanced by contrast medium. Horizontal section at the level of splenic vein is shown. Splenomegaly, dilatation of the splenic vein (*large arrow*), medial and right colic veins (*gray arrows*) are found. Renal vein (*small arrow*) is also dilated and portorenal shunt is possibly present. *Sp*, spleen; *Ao*, aorta; ×, superior mesenteric vein; *GB*, gall bladder

53 U/ml (normal <10 U/ml), indirect Coombs' test was positive, and serological test for syphilis was positive but antitreponema antibody was negative (biological false positive). On the bone marrow aspiration, nuclear cell count was 59.7 × 10^4/μl and megakaryocyte count was 208/μl. There was erythroid hyperplasia but no dysplasia of myeloid cells or chromosomal abnormality. Abdominal computed tomography (CT) scan enhanced by contrast medium (Fig. 2) disclosed a poor image of the portal vein and dilatation of the splenic vein, medial and right colic veins, renal vein, and splenomegaly. Renal vein dilatation and elevated blood ammonium level suggested the presence of possible portorenal shunt. These recanalized portal vein and collaterals were suggestive of portal vein thrombosis and portal hypertension. Pulmonary perfusion scintigram using ^{99m}Technetium-macroaggregated albumin (^{99m}Tc-MAA) showed an irregular distribution of pulmonary circulation. Gastric fiberscopy did not detect any esophageal varices. Echocardiography or brain magnetic resonance imaging disclosed neither cardiac abnormality nor ischemic brain lesions. She was diagnosed as having primary APS and autoimmune hemolytic anemia, while leukopenia and thrombocytopenia were thought to be due to hypersplenism. It was speculated that portal hypertension was caused by portal vein thrombosis due to APS, and she was given aspirin. At the same time, her facial tumor was biopsied and infiltration of round or spindle-shaped nucleated cells with an irregular focal structure and severe proliferation of connective tissue in the interstitium forming a morphea-like pattern were found (Fig. 1b). Diagnosis of BCC was made, and tumorectomy was performed successfully. Afterwards the serum titer of anti-cardiolipin β_2 glycoprotein-I antibody, LAC, and the IgG level gradually reduced, the indirect Coombs' test became negative, and C3, C4 levels, CH50, protein C activity, and coagulopathy as well as anemia gradually improved during the following 7 months without the use of corticosteroids or immunosuppressants (Table 1).

Discussion

It is known that various immunological abnormalities including APS may occur in the course of malignancy as a paraneoplastic syndrome. Paraneoplastic syndrome is a condition that occurs in the presence of neoplastic disorders, while the precise mechanism by which it occurs is not clear. Recently, it has been reported that various exogenous cytokines such as interferon (IFN)-α or interleukin-2 could trigger autoimmune phenomena including antiphospholipid antibody production.[10,11] From these findings, various cytokines produced by neoplastic cells might be associated with the pathogenesis of paraneoplastic syndrome.

On the other hand, it is known that various coagulopathies such as disseminated intravascular coagulation often occur in the course of malignancy,[12] and they may affect the progression and metastasis of the malignancy. Moreover, it has been reported that APS may be one of the contributory factors in paraneoplastic thromboembolism.[13] It has also

Table 1. Changes of antiphospholipid antibodies and immunological parameters before and after surgery

	Before resection	3 months after resection	7 months after resection
White blood cells (/μl)	1900	2800	3700
Hemoglobin (g/dl)	8.7	13.8	14.7
Platelet ($\times 10^4$/μl)	7.6	8.7	10.3
Anti-cardiolipin β2GPI antibody (U/ml) ($N < 3.5$)	25.1	22.5	12.3
PT (s)	17.0	15.8	15.0
APTT (s)	50.2	46.2	41.0
LAC ($N < 1.3$)	1.7	ND	1.5
Protein C activity ($N > 64$)	32	ND	41
IgG (mg/dl)	2080	1930	1800
C3 (mg/dl)	36	52	58
C4 (mg/dl)	<2	3	3
CH_{50} (U/ml)	<7	8.7	11.0
Coombs' test (indirect)	+	ND	−

β2GPI, β_2 glycoprotein-I; PT, prothrombin time; APTT, activated partial thromboplastin time; LAC, lupus anticoagulant; ND, not done

been reported that portal vein thrombosis often develops as a result of APS.[14–16] In the current case, portal hypertension seemed to be induced by portal vein thrombosis, which was possibly caused by APS that slowly developed 5 years after the onset of BCC. Irregular distribution of pulmonary circulation might be also associated with APS. Antiphospholipid antibody syndrome in this case was thought to be primary, because the criteria for connective tissue diseases such as SLE were not fulfilled, although there were some autoimmune phenomena such as autoimmune hemolytic anemia.

Basal cell carcinoma is known to be a skin cancer that results in ulceration and nodules. It often occurs on the face and head of elderly people, and is characterized by slow growth as in this case and destruction of the local tissue, and rarely shows metastasis to the lymph nodes. The slow growth of BCC in this case might be associated with the fact that progression of APS and thrombosis developed slowly, and this might be the reason that collateral veins through splenic and colic veins developed silently.

In this case, various immunological abnormalities might have developed during the course of BCC, for example, elevated serum levels of IgG and reduced levels of complements in addition to APS and autoimmune hemolytic anemia. The serum titers of anti-cardiolipin β_2 glycoprotein-I antibody and LAC activity gradually decreased, positive test results for syphilis disappeared, and protein C activity, which may be inhibited by anti-protein C antibody, increased after the resection of BCC. Furthermore, the serum IgG level also decreased along with the anti-cardiolipin β_2 glycoprotein-I antibody titer and Coombs' test became negative. White blood cells and platelets also increased in number up to 7 months after resection of BCC, but they remained at a similar level afterward. Improvement of some autoimmune mechanism might therefore have been associated with the increase in number of these blood cells, although the main cause of leukopenia and thrombocytopenia seems to be hypersplenism. On the other hand, the thromboembolic lesions arose after a long time, and this was thought to be the reason that lesions and collateral vessels did not disappear easily. Because the anti-cardiolipin β_2 glycoprotein-I antibody titers gradually decreased after resection of BCC, anti-coagulant therapy for APS was not added and there was no exacerbation of APS, although the clinical course of BCC and APS should be observed further.

These findings suggest that the existence of BCC, as a paraneoplastic syndrome, might have influenced immunological functions and induced APS, although it could not be determined what cytokines or mediators were involved in the pathogenesis.

References

1. Messiaen T, Lefebvre C, Lambert M. Case report: thoracic aorta thrombus with systemic embolization: a rare paraneoplastic antiphospholipid syndrome? Am J Med Sci 1996;312:303–5.
2. Yamamoto T, Ito M, Nagata S, Suzuki H, Togawa A, Nagase M, et al. Catastrophic exacerbation of antiphospholipid syndrome after lung adenocarcinoma biopsy. J Rheumatol 2000;27:2035–7.
3. Jullien V, Heudier P, Carre Y, Peyrade F, Taillan B, Tchiknavorian X, et al. Bronchopulmonary cancer, antiphospholipid syndrome and coagulation disorders. Rev Med Interne 1999;20:696–700.
4. Andrejevic S, Bonaci-Nikolic B, Bukilica M, Milivojevic G, Basanovic J, Nikolic MM. Purpura and leg ulcers in a patient with cryoglobulinaemia, non-Hodgkin's lymphoma, andantiphospholipid syndrome. Clin Exp Dermatol 2003; 28:151–3.
5. Saxena SK, Bin Salih SA, Al-Jizeeri AH, Kheir OA. Acute myeloblastic leukemia in a patient with primary antiphospholipid syndrome. Saudi Med J 2003;24:1013–5.
6. Ruffatti A, Aversa S, Del Ross T, Tonetto S, Fiorentino M, Todesco S. Antiphospholipid antibody syndrome associated with ovarian cancer. A new paraneoplastic syndrome? J Rheumatol 1994;21:2162–3.
7. Muir DF, Stevens A, Napier-Hemy RO, Fath-Ordoubadi F, Curzen N. Recurrent stent thrombosis associated with lupus anticoagulant due to renal cell carcinoma. Int J Cardiovasc Intervent 2003;5: 44–6.
8. Soltesz P, Szekanecz Z, Vegh J, Lakos G, Toth L, Szakall S, et al. Catastrophic antiphospholipid syndrome in cancer. Haematologia (Budap) 2000;30:303–11.
9. Orsino A, Schneider R, DeVeber G, Grant R, Massicotte P, Canning P, et al. Childhood acute myelomonocytic leukemia (AML-M4) presenting as catastrophic antiphospholipid antibody syndrome. J Pediatr Hematol Oncol 2004;26:327–30.
10. Becker JC, Winkler B, Klingert S, Brocker EB. Antiphospholipid syndrome associated with immunotherapy for patients with melanoma. Cancer 1994; 73:1621–4.
11. Funauchi M, Ohno M, Nozaki Y, Kinoshita K, Sugiyama M, Kanamaru A. Two injections of interferon-alpha could trigger the development of rheumatoid arthritis. Clin Exp Rheumatol 2002; 20:871.
12. Miesbach W, Sharrer I, Asherson R. Thrombotic manifestations of the antiphospholipid syndrome in patients with malignancies. Clin Rheumatol 2006;25:840–4.
13. Krmpotic D, Cikes N, Krmpotic P. Paraneoplastic syndrome associated with antiphospholipid antibodies. Lijec Vjesn 2004;126:155–60.
14. Lee HJ, Park JW, Chang JC. Mesenteric and portal venous obstruction associated with primary antiphospholipid antibody syndrome. J Gastroenterol Hepatol 1997;12:822–6.
15. Hirohata Y, Murata A, Abe S, Otsuki M. Portal vein thrombosis associated with antiphospholipid syndrome. Gastroenterology 2001;36:574–8.
16. Higa M, Kojima M, Ohnuma S, Hamanaka S, Yamamuro W, Sugiura H, et al. Portal and mesenteric vein and inferior vena cava thrombosis associated with antiphospholipid syndrome. Intern Med 2001;40:1245–9.