Acquired Factor V Inhibitor Responsive to Corticosteroids in a Patient with Double Cancers

Hitoshi Endo¹, Kiyotaka Kawauchi¹, Masahiko Tomimatsu¹, Daijiro Iga¹, Toshie Ogasawara¹, Masako Yasuyama¹, Toshihito Saito¹, Kuniaki Otsuka¹ and Motohiko Aiba²

Abstract

A 70-year-old woman suffering from HCV-related liver cirrhosis was admitted for abnormal bleeding. Laboratory findings included PT at 46.6 sec, APTT at >212 sec, factor V activity of <3%, and factor V inhibitor of 2 BU. Having experienced a persistent bleeding tendency for one month, the patient was started on prednisolone (0.8 mg/kg/day). Within a few days, the inhibitor became undetectable and clinical bleeding disappeared. Although clinical improvement was achieved, she died 6 months after the initial bleeding episode from the progression of a lung cancer. An autopsy revealed squamous cell carcinoma of the lung and hepatocellular carcinoma.

Key words: factor V inhibitor, HCV, liver cirrhosis, hepatocellular carcinoma, lung cancer

(DOI: 10.2169/internalmedicine.46.6390)

Introduction

Acquired factor V inhibitors (FVIs) have been documented since the reports by Hörder et al in 1955 (¹) and Ferguson et al in 1958 (²). In 2002, Streiff and Ness described 3 cases together with a systematic review of 126 cases retrieved through MEDLINE (³). The presence of FVIs is considered to be a rare event, while to our knowledge, 12 more cases (in English) and several cases in other languages have recently been reported.

Regarding the properties of inhibitors, it has been described that they are usually polyclonal IgG antibodies which interfere with the formation of the prothrombinase complex through binding to the C2 domain of the light chain of FV (⁴). FVIs seem to be preceded by various diseases or conditions, such as major surgery, especially when bovine thrombin or fibrin glue has been used or there has been exposure to antibiotics, autoimmune disorders, or malignant diseases. However, FVIs in conjunction with double cancers are quite rare. Here, we report an elderly patient suffering from HCV-related liver cirrhosis with HCC, who succumbed to lung cancer after successful treatment with prednisolone (PSL) for the acquired FVI.

Case Report

A 70-year-old woman was admitted to our hospital in February 1999 for the purpose of investigating an equivocal liver mass. Although angiography and needle biopsy were performed in July 1999 and May 2000, respectively, hepatocellular carcinoma (HCC) was not confirmed. Subsequently, follow-up treatment for HCV-related liver cirrhosis and hypertension was continued. Because laboratory tests revealed a high serum alanine aminotransferase (ALT) level (about 100 IU/l), the patient was given ursodesoxycholic acid orally. Other medications included amlodipine, LIVACT granules, a mixture of vitamin B, L-aspartic acid calcium, and alphacalcidol were administered for the duration of her clinical course. At the beginning of April 2001, gingival and nasal bleeding occurred spontaneously. Because her condition did not improve in spite of the administration of 4 units of fresh frozen plasma, she was hospitalized in April 2001. She had an appendectomy 50 years previously; however,
there was no personal or family history of bleeding disorders. She had been a smoker for more than 40 years.

On admission, the patient appeared pale but was otherwise in good health. Hepatomegaly, vascular spiders of the skin, and palmer erythemas of both hands were evident at the physical examination. The laboratory findings are summarized in Table 1. Coagulation studies revealed prothrombin time (PT) of 46.6 sec and activated partial thromboplastin time (APTT) of >212.0 sec, and hepaplastin test (HPT) of 61.8%. Coagulation factor assays showed a decrease in the FV activity of <3%. The titration of a specific inhibitor for FV demonstrated 2 Bethesda units (BU). Abnormal findings associated with her anemia or liver dysfunction were evident. Autoantibodies, such as anti-nuclear antibody (ANA) of ×40, lupus anticoagulant of 1.60 (normal range; <1.3), and anti-cardiolipin, β2-GPI, antibody of 4.9 U/ml (normal range; <3.5) suggested the autoimmunity as an underlying condition. A chest X-ray revealed almost normal findings. Hepatosplenomgaly was demonstrated on an abdominal CT scan: otherwise the existence of HCC was still uncertain.

The clinical course is illustrated in Fig. 1. At the end of May, the patient complained of diffuse swelling in her left calf, which was diagnosed as hematoma after an MRI examination. In the absence of a spontaneous recovery from a bleeding tendency, PSL (0.8 mg/kg/day) administration was started on the following day. She began to improve in a few days and the bleeding tendency was eliminated. On the 7th day of PSL treatment, coagulation studies revealed marked recovery; PT of 19.6 seconds and APTT of 46.2 seconds. FVI became undetectable on the 9th day. The PSL dosage was progressively reduced biweekly. Coagulation markers subsequently remained stable with an FV activity of 73%. She was discharged at the end of June.

At the end of August, the PSL dosage was increased to 30 mg/day because her PT was prolonged again. In mid-September 2001, she was re-hospitalized because of chest pain, a fever, cough, and excessive sputum production. Chest X-rays revealed a mass lesion on her right hilum. A CT scan and tumor markers suggested a lung cancer (5 cm maximum on CT scan), while a bronchoscopic study provided uncertain results. However, specific treatment was avoided because of her concomitant diseases. During the follow-up period, superior vena cava syndrome developed in mid-November and the patient expired at the end of December. She had received 20 mg/day of PSL and her FVI had remained undetectable in December.

A summary of the autopsy examination is as follows: 1.) lung cancer (well differentiated squamous cell carcinoma), 8.5×5×9 cm in size, adjacent to the right main bronchus, with metastases to the pericardium and lymph nodes of the right hilum and mediastinum (Fig. 2a and b); 2.) liver cirrhosis with moderately differentiated HCC of S8, 0.8 cm in size (Fig. 2c, d, and e); 3.) cardiomegaly and arteriosclerosis due to hypertension.

### Discussion

Knöbl and Lechner described that malignant diseases were found in 16.3% of 105 cases with FVIs (4). The underlying malignancies include multiple myeloma (4), buccal epidermoid carcinoma (5), colon cancer (6-8), pancreatic cancer (9), central nervous system tumor (10), anaplastic carcinoma (11), prostatic cancer (5, 7), metastatic liver cancer (12), and HCC (13, 14). Among those cases, only two with double cancers were documented. Bayani et al reported a case of FVI with buccal epidermoid carcinoma and prostatic cancer (5). Okajima et al introduced a case with prostatic and colonic cancers (7). Thus, a combination of lung cancer and HCC, such as that seen in the present case, is the first instance of double cancers with FVIs. FVIs had been associated with conditions such as surgical procedures.
Figure 1. Clinical course. In 1999, HCC in S8 of the liver might have been already growing, while the angiography and needle biopsy could not demonstrate its existence. Besides, it was thought that the lung cancer had appeared simultaneously with the FVIs, suggesting a relationship between the two from a chronological point of view. ALT: alanine aminotransferase, APTT: activated partial thromboplastin time, BU: Bethesda units, FV: factor V, PT: prothrombin time, UDCA: ursodesoxycholic acid.

and exposure to antibiotics in most cases; but our patient had neither undergone a surgical procedure nor received antibiotics.

Because a high signal intensity area (1 cm in diameter, figure not shown) in S8 of the liver, demonstrated by ferumoxide-enhanced MRI examination in May 1999, was considered retrospectively to be a tumor, the patient might have developed the HCC in 1999. On the other hand, the cancer of the right lung was found by a chest CT scan in September 2001. According to the formula of doubling time (15, 16), which is calculated from two tumor sizes of the initial point (5 cm in September) and the final point (9 cm in December), the lung cancer was estimated to be at least 2 cm in diameter in April 2001. However, we could not identify the tumor, probably because it was hidden by the mediastinal shadow on the chest X-ray film at that time. Because the first bleeding event occurred in April 2001, the lung cancer might have developed concomitantly, suggesting the relationship between FVI and lung cancer. It has been proposed that malignancies may cause the production of autoantibodies as paraneoplastic syndromes (17). Bayani et al (5) also referred to a link between cancer and autoimmunity and discussed the malignancy as a hypothetical cause of FVI.

In addition, a causal relationship between HCV-related liver diseases and FVIs can be considered. Generally, HCV can infect immune cells such as T- and B-cells, thus modulating the immune response (18). In fact, HCV infection has been shown to be associated with various autoimmune disorders (19). One case of HCV infection with FVIs (such as the present case) has been reported, in which a causal relationship was obscure (13). Moreover, a previous study showed the association of anti-phospholipid antibodies and FVIs (20). We observed the development of anti-phospholipid antibodies in the present case also, suggesting that an autoimmune mechanism may be involved in the development of FVIs in this patient with an HCV infection and malignancy.

In terms of therapy for FVIs with bleeding tendency, several modalities—such as platelet concentrates, intravenous immunoglobulin, plasma exchange, and immunosuppressants (e.g., corticosteroids, cyclophosphamide, and cyclosporine A)—have been employed (5, 9, 21). Streiff and Ness reviewed the treatment of patients with symptomatic FVI and recommended steroid therapy as an initial trial for those with mild-to-moderate bleeding because of the higher efficacy of corticosteroids with 74% success (3). Actually, PSL therapy was effective in suppressing FVI in the present case. Although coagulation markers such as PT and APTT indicated a transient deterioration when the PSL dosage was re-
duced, a re-escalation of PSL dosage led to a rapid normalization of abnormal coagulation values. Therefore, steroid therapy should be considered as an initial trial for FVI patients who are also suffering from malignancies.

The patient succumbed to the advanced lung cancer, although a complete resolution of FVI was maintained by PSL therapy. Because the existence of a malignancy in patients with FVIs may determine their prognosis, the screening of malignancies as underlying diseases is very important. An accumulation of such cases with a detailed investigation may contribute to clarify the mechanism by which FVIs develop in patients with malignancies.

References


© 2007 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html