Transient FV inhibitor of unknown origin in difficult clinical situation

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ABSTRACT

Acquired Factor V inhibitors are a rare condition, associated frequently with at times severe bleeding. Patients can show no symptoms and in exceptional cases thrombosis can be reported. In this article we report two cases of acquired FV inhibitors associated with thrombosis. We systematically reviewed the literature on FV inhibitors and thrombosis. A patient had acquired FV inhibitors and thrombosis. He had no bleeding and was treated with anticoagulant. Despite initial improvement, he died from legionaire’s disease. The second patient had septicemia, acquired FV inhibitors and deep vein thrombosis. The patient’s condition improved with antiocoagulation and antibiotic therapy. Ten case reports were considered in the systematic review. The median age at admission was 67. Seven patients had bleeding episodes. The median peak inhibitor titer was 2.7 BU (0.62-8) while the median FV activity was 2% (1-75). Except for 2 patients, all recovered. FV has two activities: a procoagulant action activating prothrombin, as well as an anticoagulant action activating protein C. This property could be associated with thrombosis activity. Inhibitor could also have a through effect on activated protein C. In our study, because of underlying diseases, it was not possible to clearly demonstrate that inhibitors give thrombosis. Immunosuppressive therapies were administered in cases of severe bleeding. Heparin seemed efficient for thrombosis without major bleeding. The prognosis of acquired FV inhibitors appeared to be related to the underlying disease.

Key Words: Blood coagulation factors, Hemostasis, Factor V, Thrombosis, Factor V Deficiency

1. INTRODUCTION

Acquired factor V inhibitor (AFVI) is a rare medical condition with little published literature.[1] Less than one hundred cases have been documented. AFVI is frequently associated with bleeding.[2-4] In rarer cases patients are asymptomatic. In very exceptional cases, episodes of concurrent thrombosis are reported.

There is no clear recommendation on how to deal with thrombotic occurrences associated with AFVI. In this article we report two cases of patients having develop-
oped an AFVI associated with thrombosis and review all the literature published about this association.

2. Case Presentation

Patient K, 78 years old, was admitted for heart failure. He had formerly suffered a stroke and had a history of high blood pressure (HBP). He had been treated with bisoprolol, furosemide, and esomeprazole. In 2012 his hemostatic results were normal. The initial echocardiography revealed an intra-auricular thrombus requiring anticoagulant. On his arrival and before fluindione was started, he had a subnormal prothrombine time (PT).

We observed a progressive increase of International Normalized Ratio (INR) culminating at 8.58 on day 20. PT was 44.2 seconds, factor V 2%, factor II 54% and activated Partial Thromboplastine Time (aPTT) 3.58. There was no change in blood cell counts or hepatic tests and no signs of disseminated intravascular coagulation (DIVC). The patient presented no bleeding. The most probable hypothesis was an AFVI: This was confirmed when using the Bethesda method. The AFVI was at 4 Bethesda units (BU/ml).

A complete etiological work up revealed negative (absence of use of biological glue, recent surgery, transfusion, infection, inflammatory disease, blood disease, neoplasia or autoimmune disease). No recent change in treatment apart from fluindione was reported.

In the absence of bleeding, no immunosuppressive agent was administered. For the treatment of cardiac thrombus, fluindione was switched to low molecular weight heparin (LMWH). The evolution was positive.

On day 30, PT was 14.9 seconds, FV 81% and AFVI 0.5 BU /ml. The hemostasis was slowly veering towards normal figures without ever reaching complete remission.

On day 75, the clinical evolution was marked by the onset of a hematoma at the jugular punction point of a cardiac catheter used for pulmonary hypertension screening. During this bleeding episode, PT was 16.2 seconds and FV 44% in the presence of AFVI at 1.5 BU/ml. The evolution was simple without specific treatment targeting AFVI and the anticoagulant treatment was resumed. On that day, the intracardiac thrombus was no longer visible on the echography.

On day 129, the patient had no bleeding recurrence. An oral treatment with 2.5 mg apixaban twice a day was started.

On day 154, the patient suffered septic shock because of legionaire’s disease. PT and FV plummeted due to hepatic deficiency. There was no thrombosis and no bleeding complications. The level of AFVI was below 0.4 BU/ml.

On day 162, the patient died from the sequels of this infection.

Patient L, 51 years old, was admitted for a septicemia due to Streptococcus pneumoniae with septic arthritis. His clinical history revealed recurrent deep venous thrombosis requiring long-term anticoagulation, despite a normal thrombophilia screening and a dilated cardiomyopathy. His usual treatment consisted in fluindione, rosuvastatin, ramipril and spironolactone. He was treated for this infection by systemic antibiotics (amoxicillin and clavulanic acid and gentamycin) and surgical washing of the joint. On admission under anti-vitamin K (fluindione), his PT was 16.1 seconds, FV 138%.

On day 7 after the start of the antibiotic treatment, PT and FV decreased whereas no hepatic anomaly and no DIVC were detected.

On day 9, his leg became painful and a venous Doppler ultrasound showed recent distal deep vein thrombosis. A curative anticoagulant treatment with LMWH was then started along with anti-vitamin K.

On day 13, the aPTT was 4.13, PT was 38.2 seconds and FV was 4%. The dosage of AFVI was 8 BU/ml. There was no bleeding and our search for a causative factor other that antibiotic therapy was negative. No other specific treatment was deemed necessary but anti-vitamin K was stopped.

On day 16, we stopped amoxicillin and started clindamycin and levofloxacin.

On day 26, the hemostasis results improved with FV getting towards normal at 70% and AFVI becoming undetectable. The patient was getting better. Anti-vitamin K was resumed at discharge from the hospital. A few months later, our patient had no thrombotic or bleeding episodes. FV levels remained normal.

3. Discussion

Including the two cases reported here, we gathered information on 10 patients (8 published) having suffered a thrombotic episode associated with the presence of AFVI.

Deep vein thrombosis was located in the lower limbs in 7 patients. We also reviewed an episode of cardiac thrombus, a case of gangrene and a case of stroke.

Half of the patients showed concurrently AFVI and thrombotic episodes.

Two patients had suffered from a thrombotic episode prior to the presence of the AFVI.

Three patients developed a thrombosis a few weeks after diagnosis of AFVI. At the onset of the thrombotic episode, the
TQ had been known for 8 patients with a mean value of 18.5
seconds. Factor V activity was known for 5 patients (median
value 2%, 1-75) and AFVI levels for 4 patients (median value
2.7 BU/ml, 0.62-8).

Five patients with deep vein thrombosis were treated with an
anticoagulant (heparin was added to anti-vitamin K). Intra
cardiac thrombus received heparin then a direct oral antico-
agulant.

Among the patients without anticoagulant treatment, one had
aspirin and the remaining three did not receive any antithrom-
botic treatment.

Four patients had bleeding on admission and received a spe-
cific treatment targeting the AFVI: All 4 patients were treated
with systemic corticoids. One patient was treated with intrave-
nous immunoglobulin and cyclophosphamid while another
one received plasma exchanges and azathioprin.

Two patients showed non severe bleeding under anticoagu-
lant. One patient who had not been treated with anticoagulant
showed a minor bleeding episode following surgery.

The procoagulant action of FV is due to its role in activating
prothrombin when associated with activated factor X. The
inactivation of FV is mainly driven by the action of protein
C and protein S.[4] But factor V shows also an anticoagulant
activity: This activity is due to its synergy with activated
protein C enabling the suppression of activated factor VIII.[4]

The possibility of an acquired deficit in factor V must be
raised in case of lowered TP and extended aPTT connected
to a decrease of FV activity in the absence of other putative
causes. The calculation of the inhibitor’s titer may be done
by adding control plasma to the patient’s plasma. One BU
is the quantity of inhibitor that can neutralize 50% of the
factor.[4]

In our sample, the mean FV activity was 3.5% as opposed to
1% in the literature.[3] Ang et al.[2] reported in their work an
association between severe bleeding and the FV rate. In our
series, the mean inhibitor rate was 4 BU (as opposed to 19
BU in the work of Franchini et al.[3] Due to the small scale
of our sample, it was not possible to point a link between
biological values and the risk of bleeding in our study.

The etiological factors of AFVI can be set in 5 categories:
Use of biological glue, surgery, transfusion, other causes
(cancer, infections . . . ) or idiopathic (bearing a bad outcome).

In our review, the factors inducing the onset of the inhibitor
seemed rather clear. We found 3 cases of infection, 3 cases
of cancer, 2 cases of lymphoma, 3 cases of surgery and 2 cases
of autoimmune diseases. In 2 cases no obvious associated
factor could be found. Our results bore close similitudes
to those reported in the two main reviews previously pub-
lished.[2, 3]

For 3 patients, the AFVI appeared after the prescription of
anti-vitamin K. A few case reports also described the on-
set of AFVI after treatment with anti-vitamin K, raising the
question of its immutability.[5, 6] Anti-vitamin K should thus
be used with caution in the context of AFVI.

The potentially thrombogenic role of these auto-antibodies
was recently pointed in the case of a patient with repetitive
thrombotic episodes.[7] This patient showed a resistance to
activated protein C, without mutation of Leiden FV but with
the presence of an AFVI. The possible action of the antibody
on activated protein C was pointed. The other possibility
was an inhibition of the anticoagulant action of FV through
a direct effect of the antibody on this factor. The last possi-
bility was that AFVI may show lupus-like anti-phospholipid
properties.[8] Due to the elevated venous thrombotic risk of
the patients considered in our article, it was impossible to
establish a clear and definitive link between the AFVI and
the onset of thrombotic episodes.

Specific treatments targeting AFVI were administrated to 4
patients. All these patients recovered with the disappearance
of AFVI. A faster clearance of the antibody was obtained
in patients with bleeding when treated with a specific ther-
apy[2, 3] but this treatment did not influence biological or
clinical evolution for asymptomatic patients. No current liter-
ature can put forward the safest and most efficient therapeutic
strategy in that context.

One patient received aspirin for the treatment of arterial
thrombosis (stroke).[9] Three other patients presented serious
bleeding and received a specific treatment without anticoagu-
lant.[10–12] All of these 4 patients evolved favorably. The
remaining six patients were treated with heparin (LMWH
or unfractionated heparin) during the initial phase followed
by anti-vitamin K or oral anticoagulants.[6, 13–15] The treat-
ment with heparin helped towards a favorable evolution of
thrombosis.

Two patients showed a bleeding complication with heparin
(secondary to an invasive procedure) but no transfusion was
needed. The other patients did not show any bleeding under
anticoagulant treatment. The use of heparin with a close bi-
ological monitoring in the acute phase of thrombosis appeared
in this series as a safe strategy in the context of AFVI.

In our review, 2 patients died but their deaths were not caused
by a thrombotic or bleeding accident (in both cases death was
caused by a septic shock).[10] There was evident clinical and
biological improved state of health for all remaining patients.
In the literature, as well as in your study, prognosis was clearly more linked to the underlying disease than to the consequences of AFVI.

4. CONCLUSION
This review confirms the rare occurrence of AFVI associated with thrombotic episodes. The clinical picture is many-faceted but often associated with bleeding. The etiological role of AFVI in the onset of thrombosis is often hard to demonstrate. The treatment of thrombosis is not consensual and is mainly based on the introduction of an anticoagulant (heparin in the initial phase) with a relatively good tolerance in our series. Bleeding can sometimes require the use of specific treatments. The prognosis is clearly linked with underlying pathologies.

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CONFLICTS OF INTEREST DISCLOSURE
The authors have declared no conflicts of interest.

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