

A physician or group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary

Not as sweet as honey: A rare case of an apparent factor V “inhibitor” in association with bee sting anaphylaxis

Elisabeth Farhat¹ | Elizabeth Tegg¹ | Soma Mohammed¹ | Elzbieta Grzechnik¹ |

Emmanuel J. Favaloro^{1,2} 

¹Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), NSW Health Pathology, Westmead Hospital, Westmead, NSW, Australia; ²Sydney Centres for Thrombosis and Haemostasis, Westmead, NSW, Australia

Correspondence

E.J. Favaloro, Department of Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, NSW, 2145, Australia.
Email: emmanuel.favaloro@health.nsw.gov.au

1 | CASE PRESENTATION

A 25 yo, previously well male, presented with anaphylactic shock following a honeybee sting while gardening at his home in Sydney, Australia. After being stung on the lip by a bee the patient was witnessed, by his partner, to develop rapid facial swelling and erythema before vomiting and collapsing with evidence of respiratory distress. On the arrival of emergency services there was significant facial and airway edema, making intubation difficult. The patient was transferred to our facility (Westmead Hospital) after a period of prolonged hypoxia and hypotension, having received intramuscular and intravenous adrenaline on route to hospital, with minimal effect. A definitive airway was established with endotracheal intubation upon arrival in the Emergency department. Initial hematology review demonstrated a relative polycythemia, leucocytosis, and normal platelet count. Biochemistry showed a severe mixed respiratory and metabolic acidosis with normal renal function and mildly deranged liver function tests (Table 1). Computer tomography (CT) of the brain showed extensive low-density changes in the white matter scattered throughout both cerebral hemispheres, consistent with hypoxic brain injury.

Anaphylaxis is an acute, severe, life threatening type I hypersensitivity reaction leading to a systemic response caused by the immediate release of immune and inflammatory mediators.¹ The mechanism of anaphylaxis involves exposure to an allergen (most commonly food, drugs or insect venom) in a presensitized individual, which interacts with allergen-specific immunoglobulin E (IgE) bound to mast cells and/or basophils causing rapid degranulation and the release of cytokines including histamine, prostaglandin D₂, leukotrienes, platelet-activating factor, tryptase, nitric oxide, and eosinophil/neutrophil chemotactic factors.² These mediators have multi-system effects including smooth muscle spasm in the respiratory and gastrointestinal tracts, vasodilation,

increased vascular permeability, mucous hypersecretion, myocardial dysfunction that lead to hypotension and cardiovascular collapse.

The patient was transferred to the intensive care unit (ICU), ventilated and was continued on an intravenous adrenaline infusion for treatment of anaphylactic shock. Although there were no evident signs of bleeding, as standard for ICU admissions, several routine hemostasis tests (representing the first coagulation profile performed) were ordered following the patient's transfer, now three hours after arrival at hospital. These were critically deranged, as follows: prothrombin time (PT) >120 seconds (normal: 11–18 seconds); activated partial thromboplastin time (APTT) >150 seconds (normal 24–38 seconds) (Figure 1). Accompanying hematology results showed normalization of hemoglobin to 155 g/L and a twenty-percent drop in platelet count to $198 \times 10^9/L$. Additional routine hemostasis tests were added by reflex, with the following results: thrombin time (TT) >100 seconds (normal: 10–17 seconds), fibrinogen <0.6 g/L (normal 1.8–4.4 g/L), and D-dimer 1.89 mg/L (positive). A serum tryptase was also performed at 3 hours post admission, yielding a result of >200 ug/L (normal range 0.0–11.4).

The initial coagulation profile, as routinely performed on patient admission to the ICU, yielding such profound prolongation of clotting times was an unexpected finding in the absence of clinical bleeding. Initial differential diagnoses for the deranged coagulation profile included possible heparin contamination (from recent arterial line insertion), an under-filled collection tube, a clotted sample or disseminated intravascular coagulopathy (DIC). DIC was particularly considered based on the low fibrinogen and positive D-dimer; indeed, the fibrinogen level reported (<0.6 g/L) reflects the lower limit of detection of our standard assay, and thus could also have reflected a (virtual) absence of fibrinogen. However, some other differentials or complicating factors needed to also be excluded, given overall test findings. DIC is an acquired

TABLE 1 Initial presentation test results (hematology and biochemistry)

Test (and units)	Result	Normal Reference Range
Hematology		
Haemoglobin (g/L)	185 (H)	130–180
White cell count ($\times 10^9/L$)	17.0 (H)	3.7–9.5
Platelets ($\times 10^9/L$)	246	150–400
Biochemistry		
pH	6.85 (L)	7.35–7.45
Bicarbonate (mmol/L)	15 (L)	22–28
Lactate (mmol/L)	16.0 (H)	< 2
Creatinine ($\mu\text{mol/L}$)	110	60–110
ALT (U/L)	67 (H)	≤ 40
AST	76 (H)	≤ 40

H = high; L = low; bold = abnormal.

syndrome characterized by activation of the coagulation pathways resulting in formation of intravascular thrombi and depletion of platelets and coagulation factors leading to spontaneous, generalized bleeding.³ Anaphylaxis is a rare but well described cause of DIC, mediated through the release of platelet activating factor following degranulation of mast cells and basophils.⁴ The high total serum tryptase identified was consistent with mast cell degranulation and the diagnosed anaphylaxis. Although high serum tryptase may alternatively suggest systemic mastocytosis, the mean serum tryptase in systemic mastocytosis is typically lower at $\sim 70 \mu\text{g/L}$.⁵ Moreover, the diagnosis of anaphylaxis was clear to us given the background clinical history.

The coagulation profile was repeated. During this time, the patient developed hematuria and haematochezia and was also issued 4 units of fresh frozen plasma (FFP) and 2 units of cryoprecipitate (apheresis) for the management of his presumptive DIC. Repeat coagulation profile (sample 2, Figure 1, taken at 4 hours post admission, and prior to administration of products) was congruent with initial values (APTT >150 s; PT 86 s; TT >100 s; fibrinogen <0.6 g/L; D-dimer 1.89 mg/L (positive)). An “immediate” (i.e., nonincubated) mixing study was also performed at this stage—this showed correction of PT to 15 seconds but ongoing prolongation of APTT at >150 seconds following 50/50 mix. Personal and family history obtained via the patient's next of kin did not reveal any prior history of abnormal bleeding or known hereditary bleeding disorder. The patient was not on any regular medications and had no history of illicit drug use. At the time of presentation, it was identified that a bee had stung him, although there was no history of previous allergy to same.

It was now becoming clear that the primary differential diagnosis of DIC was unlikely to be the sole cause of the prolonged clotting times in our case. As a consumptive coagulopathy, DIC leads to prolonged clotting times secondary to pan-factor deficiencies that are expected to correct on a 50/50 mix with normal patient plasma.³ The persistently

prolonged APTT following 50/50 mix raised other possibilities or confounders for the differential diagnosis, including a factor inhibitor(s), severe heparin contamination and/or the presence of a phospholipid-interfering substance.

As this was out of normal work hours, a technician was specifically called in to perform heparin and factor assays on the initial sample. Heparin was detected at 0.18 U/mL (STA Liquid Anti-Xa, Diagnostica Stago, Sydney, Australia). There was also a global reduction in factor levels, with undetectable V, VIII, IX, and XI (Table 2; Figure 1).

The titer of heparin that was detected was determined to be insufficient on its own to have caused the previously noted extendedly prolonged routine test results, and another quite striking abnormality—the undetectable levels of factors V, VIII, IX, and XI. The PT reagent used in our laboratory (Neoplastin CI Plus; Diagnostica Stago, Sydney, Australia) is known to be resistant to unfractionated heparin up to 1 U/mL and low molecular weight heparin to 1.5 U/mL, and would not have been prolonged (initially at >120 seconds) based on the heparin alone. Also, at the heparin level detected, the APTT (using Actin FS, Siemens, Sydney, Australia) would not be expected to be maximally prolonged (>150 seconds). With the acquisition of these results, together with the abnormal mix-APTT test results on the second sample, it appeared increasingly probable that some sort of factor “inhibitor” was at play, as primarily causing the significant abnormalities in laboratory coagulation profiles.

The technician was requested to progress an investigation into possible factor inhibitors, focusing primarily on the “absent” factors (V, VIII, IX, and XI). As the initial two samples were now depleted, due to automated instrument reruns (related to the grossly deranged coagulation times), and performance of mixing studies and factor assays, the inhibitor assays were progressed on the third sample (taken just over 6 hours after patient admission; Figure 1). At the time of testing, it was believed that this had still been collected prior to administration of transfused products. Given the identified absent FVIII on early samples, and because a FVIII inhibitor could not as yet be fully ruled out, the inhibitor assays were performed as an incubated (30°C, 2 hours) Bethesda assay.⁶ As there was also progressive clinical bleeding with ongoing haematochezia, hematuria and oral mucosal bleeding in the presence of persistently prolonged clotting times, another 8 units of FFP was ordered and then administered and the coagulation and factor profiles repeated over time (Figure 1; Table 1). An apparent factor V inhibitor was detected at 40 Bethesda units, whereas inhibitors to other factors, including FVIII, were not detected (Figure 2). The factor profile post transfusion interestingly showed some correction of factor levels, albeit remaining lowest for factor V (Figure 1). Ongoing plasma product was given (while the factor V inhibitor was being identified), and clinical bleeding was controlled, with improvement in the APTT first seen at 10 hours after arrival at hospital (Figure 1). Factor levels performed on all available subsequent samples by that time are also shown in Figure 1. Unfortunately, the patient's clinical status declined with loss of brainstem reflexes despite improvement in haemodynamics. A repeat CT brain showed progression of global mass effect and generalized loss of grey-white matter differentiation with evidence of significant cerebral tonsillar

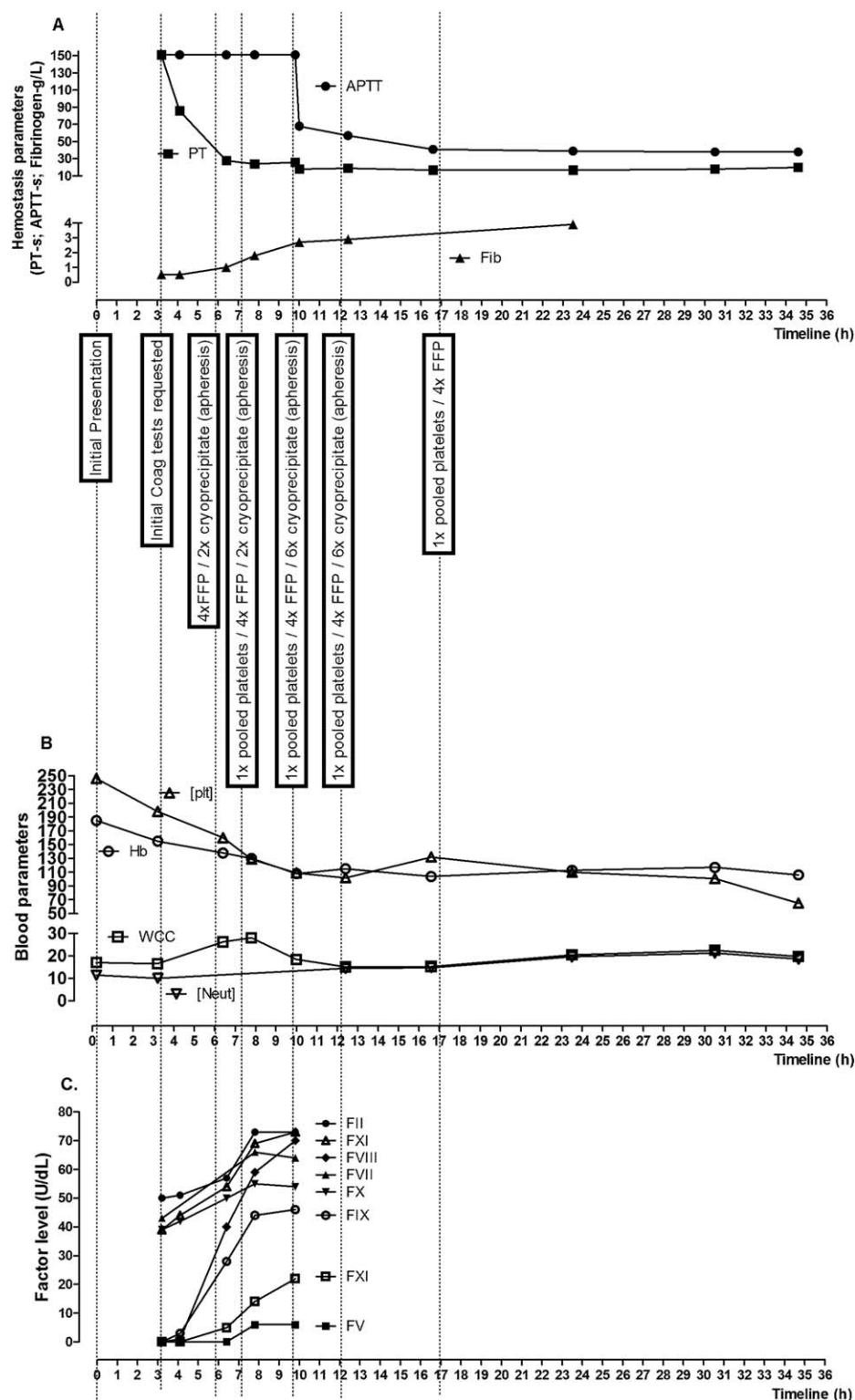


FIGURE 1 Timeline of case presentation, with results of laboratory tests and products transfused also shown

herniation. There was concurrent evidence of ischemic hepatitis (ALT 216 U/L, AST 619 U/L, bilirubin 22 μ mol/L) and myocardial damage (hsTroponin I 3511 ng/L). In the absence of ongoing plasma product administration, the patient's coagulation profile almost normalized 18 hours after presentation with results as follows: PT 17s, APTT 41s and platelet count 132×10^9 /L (Figure 1). The serum tryptase was

reassessed at 40 hours post presentation and yielded a level of 47.6 μ g/L. Allergy testing at this time confirmed the presence of a specific IgE to the honeybee, but no evidence of IgE to European or Paper wasp, confirming the initial report of a bee sting. Unfortunately, the patient was pronounced brain dead and underwent organ retrieval shortly afterwards.

TABLE 2 Factor levels

Factor	Pretransfusion (U/dL)	Post-transfusion with FFP and cryoprecipitate (U/dL)	Reference range (U/dL)
II	50	73	65–130
V	0	6	55–140
VII	43	64	60–140
VIII	0	70	45–180
IX	0	46	60–150
X	39	54	60–140
XI	0	22	50–140
XII	39	73	40–190

Bold values represent low (i.e., abnormal) values. Factors II, V, VII, and X performed as a modified PT, using same reagent as the PT screen. Factors VIII, IX, XI, and XII performed as a modified APTT, using same reagent as the APTT screen. Initial pretransfusion sample is first coagulation sample at 3 hours post presentation (Figure 1); post transfusion sample is that at 10 hours post presentation (Figure 1).

2 | DISCUSSION

Historically, most acquired factor V (FV) inhibitors, including those from our geography,⁷ have been associated with previous exposure to topical bovine thrombin. The bovine thrombin product, which was previously used as an adjuvant hemostatic agent for surgical procedures, contained trace amounts of bovine FV, which acted as a stimulus for the formation anti-bovine FV inhibitors that then cross-reacted with human FV.⁸ Formation of such inhibitors are unlikely these days given the general removal of bovine thrombin products from surgical use. A systematic review of acquired FV inhibitors, published in 2011,⁹ reviewed 78 previous case reports of patients with FV inhibitors in the absence of previous exposure to bovine thrombin. In a majority of the cases reviewed the patients had an underlying autoimmune disorder (13%) or solid organ/hematological malignancy (22%); but the most prevalent association common to 42% of the cases reviewed, was use of recent antibiotic therapy, especially beta-lactams, aminoglycosides, cephalosporins, tetracyclines, and quinolones.

Ratnoff et al. reported profuse hemostatic defects in a case of wasp sting anaphylaxis in 1983.¹⁰ In the case they presented, there was significant prolongation of the PT and APTT, as well as profound reductions in the levels of FV, fibrinogen and high molecular weight kininogen. It was concluded that there was an inhibitor present that interfered with the action of thrombin. However, specific factor inhibitor levels were not reported.

The venom of the honeybee (*Apis mellifera*) contains phospholipase A₂, which in vitro has been shown to influence all phases of the coagulation cascade; with reduction in the activity of factors II, V, and VIII demonstrated after in vitro addition to human plasma or subcutaneous administration of phospholipase A₂ in animal models.^{11,12} The in-vitro testing performed by Petroianu et al. identified greatest effects on FVIII, with reduced effects on FII and FV.¹¹ Indeed, this study was able to show reduction in FVIII activity to 1 U/dL, whereas FII and FV levels

in treated plasma remained above 50 U/dL. Consistent with these factor findings, effects were also greatest on APTT than PT. Another interesting study was reported by Mounier et al.,¹³ who evaluated different structure function relationships of human group IIA phospholipase A₂ (hGIIA). In addition to being present in animal venoms (including bee sting venom), phospholipase A₂ is present in various human cell types, including macrophages, eosinophils and platelets, and has been shown to have effects on hemostasis. In this study, hGIIA, and various forms created by site-directed mutagenesis of hGIIA, were evaluated for effects on prothrombinase activity, in comparison with bee venom (*Apis mellifera*), with the latter much more capable of inhibition of prothrombinase activity, particularly in the presence of phospholipids. The prothrombinase complex consists of calcium, phospholipids, and activated FX (FXa) and FV (FVa). No information was available in that study on which components of the prothrombinase complex are most affected by phospholipase A₂. In a later review, the same group further delineated the expected consequences of phospholipase A₂ on hemostasis.¹⁴ Strikingly, they reported that some isoforms of phospholipase A₂ may compete with FVa for binding to FXa.

Another case, dealing with wasp sting, reflected on the in-vivo release of heparin after wasp sting anaphylaxis.¹⁵ In this case, the authors identified detectable anti-Xa activity ("equivalent to a therapeutic heparin range"), despite the patient having not received any heparin. The case also presented with unclottable APTT (>200 seconds), low FV (24 U/dL), low FXI (32 U/dL), elevated D-Dimers (0.99 mg/L), but normal FVIII (144 U/dL) and near normal PT (14.6 seconds; normal range 7.0–10.1). The authors attributed these findings to activation of mast cells that released both heparin and tryptase. Although they could not totally discount a DIC like event, they proposed that the observed hemostasis derangement was mostly attributable to the released heparin and tryptase, with the latter identified at a level >200 ug/L (being similar to our case). Indeed, the tryptase was proposed to cleave the α and β chains of fibrinogen, and potentially also act "directly on the fibrinolytic pathway by activating the single-chain urinary type plasminogen activator (scu-PA or pro-urokinase), resulting in conversion of

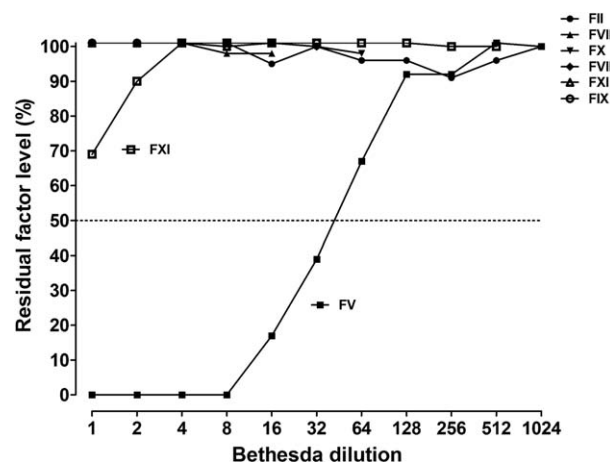


FIGURE 2 Results of the Bethesda inhibitor assay, as performed on the third sample, using an incubated test process, at 6 hours post presentation

plasminogen into plasmin and therefore degradation of fibrinogen and other coagulation factors." The effects of mast cell released tryptase on fibrinogenolysis and the fibrinolytic pathway are further highlighted in other early literature.^{16,17} The finding of fibrinogenolysis or isolated prolongation of the APTT following wasp sting was also highlighted in other case reports.^{18,19}

Our case highlights a complex clinical situation where the laboratory finding of a "factor V inhibitor" was entirely unexpected, catching both the clinical and laboratory staff by surprise. As previously discussed, the derangement in coagulation profile observed in our patient was initially considered to be secondary to DIC, otherwise well described in cases of severe anaphylaxis. Initial suspicion around DIC was strongly supported by positivity for D-dimer, low (near) absent fibrinogen levels, and generalized low factor levels. In retrospect, we believe there was an element of DIC in this case, which confounded the coagulation abnormalities observed, with most factor levels also observed to increment with administration of FFP. Also confounding the coagulation findings in this case was the finding of heparin "contamination," albeit not at a level (0.18 U/mL) that would entirely explain the coagulation derangements seen. Thus, this heparin level would not be expected to cause any prolongation of PT, nor the severe prolongation of APTT observed, nor explain the abnormal APTT-mix. It would, however, likely contribute to some prolongation of the TT and APTT. Although the level of heparin detected in our assay cannot be entirely proven to be due to heparin, and not due (at least in part) to some other interferant, we can exclude most of the reported assay interferants, including bilirubin, as such levels were within the normal range.

Nevertheless, perhaps the most surprising finding in our case was the apparent specific "FV inhibitor" (Figure 2), potentially time-dependent in nature, given the eventual normalization of hemostasis without specific anti-inhibitor treatment. We cannot fully explain our findings, but offer some additional commentary. A FV inhibitor would be expected to prolong the PT more than the APTT. Moreover, normalization of the PT upon immediate mixing, contrasting the nonnormalization of the APTT upon immediate mixing, is also contrary to expectations. Indeed, the expectation would be that the PT would not correct on immediate mixing, which is our experience in the past.⁷ Lupus inhibitor testing was performed on a later sample to help explain our findings, but was found to be negative. C-reactive protein (CRP) testing was also performed, and was initially within normal limits at initial presentation, but was elevated at 50 mg/L (normal <3 mg/L) at 16 hours post presentation. Given normal values at presentation, and no subsequent testing until 16 hours, it is difficult to know if CRP was also involved, at least in part, in the prolonged APTT/noncorrected mix test result.

Perhaps also pertinent is that the PT and APTT mixing studies were performed as immediate mixes, whereas the inhibitor assay was performed as an incubated Bethesda assay, since at that time we reflected on the absence of FVIII and could not fully exclude a FVIII inhibitor. With the benefit of informed hindsight, we also now believe that rather than the inhibitor assay being performed on a transfusion naïve sample, some product had probably been prior to the collected (third) sample. We base this on the timeline of transfused products, the

time of sample collection, and that on this sample, the FVIII level had reached nearly 40 U/dL (Figure 1). Based on product composition and timeline interrogation, we suspect that this sample was taken after at least one FFP and cryoprecipitate had been transfused. Also with the benefit of informed hindsight, it is likely that the identified FV inhibitor was not an antibody mediated inhibitor. The primary reasons for this belief are the time course of the "inhibitor," which seemed to disappear within the time-frame of the case, and the lack of concordance of an anti-FV antibody effect with the normal immediate PT mix. Accordingly, it remains more likely that the "specific FV inhibitor" could have been an unusual time-dependent event, potentially related to phospholipase. Here, we may conjecture to exist two time-dependent events, the first potentially being the bee venom phospholipase itself, potentially supplemented by subsequent "anaphylaxis/immune mediated" human phospholipase release, and subsequent effects on hemostasis, including inhibition of the prothrombinase complex, and reduction of some factors, including FVIII. We were intrigued to also recently discover that some isoforms of phospholipase A2 may compete with FVa for binding to FXa.¹⁴

The apparent level of FV inhibitor, at 40 BU, could also be due to the time incubated nature of our Bethesda assay. In hindsight, we would, if we were able, investigate for any differential in FV inhibitor level between incubated and nonincubated Bethesda assays. The FV inhibitor assay would not distinguish between inhibition of FV or FVa. We cannot identify if this "specific FV inhibitor" is an effect of phospholipids per se, but if so, cannot explain why FV was so specifically affected, given that phospholipids enhance hemostasis elsewhere in the "coagulation cascade," and an effect on phospholipids per se should also manifest with effects on other factors.

Also with the benefit of informed hindsight, it is similarly possible that the released tryptase itself (>200 ug/L at one point, and similar to that reported by Lombardini et al.¹⁵), may potentially have contributed to deranging hemostasis by direct effects on fibrinogenolysis and the fibrinolytic pathway.¹⁶⁻¹⁸ The derangement in hemostasis we observed was possibly further complicated by a DIC-like event, in particular given the positive D-dimer. Heparin, either as provided ex-vivo in the arterial line, or as potentially released from mast cells, contributed to the hemostasis derangements seen, in particular contributing to the prolonged APTT, 1:1 APTT mix and thrombin time.

Despite the discontinuation of plasma product administration, the abnormal coagulation profile almost completely corrected at 20 hours post envenomation. In summary, it could thus be postulated that exposure to honey bee venom had induced a (?short lasting/time limited) cross-reacting antibody to human FV or FVa or alternatively, and more likely, that the venom itself contained or otherwise induced a "FV-like inhibitor" that later "resolved." Certainly, none of the previous case reports we identified, either related to bee or to wasp sting, had exactly the same hemostasis picture as our case, and while some reported low factor V levels, the reported levels did not fall to zero, as in our case, and none of the previous studies assessed for the presence of a FV-inhibitor. Also important to recognize is that this case progressed from presentation to termination within a very short time frame. Indeed, the patient was pronounced brain dead within 40 hours of presentation,

and despite the considerable efforts of clinical and laboratory staff aiming for a better outcome. The case also progressed after normal work hours and required call backs and close collaboration between clinical and laboratory staff, as well as quick decisions. Depletion of initial samples caused reliance on later samples, and pro-hemostatic treatment would eventually compromise the utility of subsequent samples to resolve the conflicting laboratory findings we encountered. Given clinical urgency, some clinical decisions were necessarily undertaken prior to results of specialized laboratory testing being available. Nevertheless, given the speed that the case progressed, it is unlikely that different clinical decisions would have changed the course of this case. To help provide context, the timeline of the case is shown in Figure 1.

Finally, it is noted that the current report provides a different perspective to that described by Pollyea and colleagues,²⁰ who reported in this journal nearly a decade ago on a case of anaphylaxis due to an attack of yellow jackets, and the identification of systemic mastocytosis (SM) and monoclonal mast cell activation syndrome in that patient. It is hoped that the current report, which may reflect a kind of “perfect storm” event, will function as an impetus to further evaluate other pathology associated with insect stings, especially hemostatic abnormalities that occur with envenomation by the honeybee.

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ORCID

Emmanuel J. Favaloro  <http://orcid.org/0000-0002-2103-1661>

REFERENCES

- [1] Kemp S, Lockey R. Anaphylaxis: a review of causes and mechanisms. *J Allergy Clin Immunol*. 2002;110(3):341–348.
- [2] Finkelman F. Anaphylaxis: lessons from mouse models. *J Allergy Clin Immunol*. 2007;120(3):506–515.
- [3] Favaloro EJ. Laboratory testing in disseminated intravascular coagulation. *Semin Thromb Hemost*. 2010;36(04):458–467.
- [4] Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol*. 2008;153(S1):7–11.
- [5] Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am*. 2006;26(3):451–463.
- [6] Kershaw G. Detection and Measurement of Factor Inhibitors. *Methods Mol Biol*. 2017;1646:295–304.
- [7] Favaloro EJ, Posen J, Ramakrishna R. Factor V inhibitors: rare or not so uncommon? A multilaboratory investigation. *Blood Coagul Fibrinolysis*. 2004;15(8):637–647.
- [8] Knöbl P, Lechner K. Acquired factor V inhibitors. *Baillieres Clin Haematol*. 1998;11(2):305–318.
- [9] Franchini M, Lippi G. Acquired factor V inhibitors: a systematic review. *J Thromb Thrombolysis*. 2011;31(4):449–457.
- [10] Ratnoff OD, Nossel HL. Wasp sting anaphylaxis. *Blood*. 1983;61(1):132–139.
- [11] Petroianu G, Liu J, Helfrich U, Maleck W, Rufer R. Phospholipase A2-induced coagulation abnormalities after bee sting. *Am J Emerg Med*. 2000;18(1):22–27.
- [12] Prado M, Solano-Trejos G, Lomonte B. Acute physiopathological effects of honeybee (*Apis mellifera*) envenoming by subcutaneous route in a mouse model. *Toxicon*. 2010;56(6):1007–1017.
- [13] Mounier CM, Luchetta P, Lecut C, et al. Basic residues of human group IIA phospholipase A2 are important for binding to factor Xa and prothrombinase inhibition comparison with other mammalian secreted phospholipases A2. *Eur J Biochem*. 2000;267(16):4960–4969.
- [14] Mounier CM, Bon C, Kini RM. Anticoagulant venom and mammalian secreted phospholipases A(2): protein- versus phospholipid-dependent mechanism of action. *Pathophysiol Haemost Thromb*. 2001;31(3–6):279–287.
- [15] Lombardini C, Helia RE, Boehlen F, Merlani P. Heparinization” and hyperfibrinolysis by wasp sting. *Am J Emerg Med*. 2009;27(9):1176.e1–1173.
- [16] Thomas VA, Wheelless CJ, Stack MS, Johnson DA. Human mast cell tryptase fibrinolysis: kinetics, anticoagulation mechanism, and cell adhesion disruption. *Biochemistry*. 1998;37(8):2291.
- [17] Stack MS, Johnson DA. Human mast cell tryptase activates single-chain urinary-type plasminogen activator (pro-urokinase). *J Biol Chem*. 1994;269:9416–9419.
- [18] Mazzi G, Raineri A, Lacava E, De Roia D, Santarossa L, Orazi BM. Primary hyperfibrinolysis in a patient with anaphylactic shock. *Haematologica*. 1994;79:283–285.
- [19] Wang JL, Shen EY, Ho MY. Isolated prolongation of activated partial thromboplastin time following wasp sting. *Acta Paediatr Taiwan*. 2005;46(3):164–165.
- [20] Pollyea DA, George TI, Corless C, Gotlib J. When yellow jackets attack: recurrent and severe anaphylactic reactions to insect bites and stings. *Am J Hematol*. 2009;84(12):843–846.

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