DFASM3 – FollowUp 06 *Persistent Bleeding* Transcript

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Dr. WENDY TURR, attending physician at Brigham and Women's urgent care clinic, is checking on Dr. DAVID FINKLE, a 2nd year resident.

DAVID FINKLE: Hello, Dr. Turr. You wanted to see me?

WENDY TURR: Hello, David. Yes. What can you tell me about the patient you have been examining this evening, Ms. Lucy Evergreen?

DAVID FINKLE: Right, yeah. She is a 62-year old patient who presented to the clinic with **gingival bleeding** after periodontal **scaling** of her lower-right second **molar**. She had **undergone** the procedure 5 hours **before presentation** and the bleeding had persisted **despite** the application of pressure and ice. Ms Evergreen recalled having had a similar episode approximately 6 months ago, also after a periodontal procedure, in which bleeding had stopped only after firm pressure had been applied and held for 6 hours. She was otherwise in her usual state of good health. She reported no easy **bruising**, epistaxis, rectal bleeding, hematuria, **weakness**, fatigue, **light-headedness**, fever, arthralgia, dyspnea, jaundice, abdominal--

WENDY TURR: Alright, alright. Did you get her history?

DAVID FINKLE: Yes. She has hypertension, she had **deep-vein thrombosis** in the legs 20 years ago, she had cosmetic **blepharoplasty** without bleeding complications when she was in her 20s, and arthroscopic repair of **meniscal tear** in the left knee without bleeding complications a year ago. She also had an uncomplicated spontaneous vaginal delivery. She used to smoke but quit 30 years ago and only drinks alcohol very infrequently. She has no family history of bleeding diathesis. Her mother is 88 and in good health, but her father died of lung cancer at the age of 62 and her brother was diagnosed with colorectal cancer at the age of 57.

WENDY TURR: Any medications or allergies?

DAVID FINKLE: She has no allergies. She takes a thiazide diuretic, and she took an aspirin pill 2 hours before the dental procedure.

WENDY TURR: Ok, let's talk about your examination. Vital signs?

DAVID FINKLE: Heart rate 80, BP 128/76.

WENDY TURR: Oral cavity?

DAVID FINKLE: There was slow **oozing** of blood near her lower-right second molar, without visible mucosal laceration. I could detect no oral petechiae, **bullae** or ulcers.

WENDY TURR: Any other remarkable findings?

DAVID FINKLE: Not really. Everything was normal: chest, heart, **lymph nodes**, abdomen and rectum (which was negative for **occult blood**). Legs were warm with **brisk** capillary **refill**. All was fine.

WENDY TURR: Given the patient's history, is her condition more **likely** to be acquired or genetic?

DAVID FINKLE: Hmm. I would say acquired because the patient underwent clinically significant hemostatic challenges in the past, including childbirth and orthopaedic surgery, without bleeding complications.

WENDY TURR: And is her condition more likely to be related to a coagulation factor disorder or a platelet disorder?

DAVID FINKLE: I think a platelet disorder.

WENDY TURR: Any particular reason?

DAVID FINKLE: Hum – I – uh...

WENDY TURR: Well, your **gut feeling** is correct. Mucocutaneous bleeding, such as epistaxis, menorrhagia or gingival bleeding, as seen in this patient, is typical of disorders of primary hemostasis, such as qualitative platelet disorders and von Willebrand's disease. In contrast, **unprovoked hemarthroses** and **deep soft-tissue hematomas** are characteristic of disorders of coagulation factor deficiency, such as haemophilia. Now, what are the possible causes of the patient's condition?

DAVID FINKLE: Well, as you said, acquired von Willebrand's disease is a possibility. I also thought that liver disease, thrombocytopenia and uremia would be appropriate to include in the differential diagnosis.

WENDY TURR: And so is factor VIII inhibitor, which is an acquired coagulation factor disorder that can manifest as clinical bleeding. What tests have you ordered, and do you have the results?

DAVID FINKLE: I ordered a few tests, including a **CBC.** The monocytes are high at 13% and the hematocrit percentage is low at 31.8. Her creatinine levels are also elevated at 1.4, and so are her total protein levels at 8.6. The activated partial-thromboplastin time is prolonged at 49.6. The rest, including **BUN**, albumin, thyrotropin, **platelet count**, white-cell count, prothrombin time and **MCV** is normal.

WENDY TURR: And at this stage, which disorders best fit this patient's presentation out of the five we selected for our differential diagnosis?

DAVID FINKLE: Hrm. Given her results, and the fact that her **aPTT** is prolonged but she has a normal **PT**, normal albumin level and platelet count, and has had no known **exposure** to **unfractionated heparin**, I think she could either have a **deficiency** or an inhibitor of a factor in the intrinsic coagulation **pathway**, such as Factor VIII. And von Willebrand factor **binds** factor VIII and increases its **half-life** in the circulation, so a deficiency of **vWF** can result in a prolonged aPTT.

WENDY TURR: That's actually quite good, well done. So we now need **further** testing to determine whether a factor VIII inhibitor or von Willebrand's disease is **involved**. What will you order?

DAVID FINKLE: Factor VIII activity **assay**, aPTT after mixing of the patient's plasma and normal plasma in a 1:1 ratio, von Willebrand factor antigen level and vWF multimer gel electrophoresis.

WENDY TURR: Yes, but do not forget ristocetin cofactor activity. Let me know what the results are before administering treatment, will you?

DAVID FINKLE: Yes, Dr. Turr, of course.

The next day, DAVID FINKLE returns with the results of the tests.

DAVID FINKLE: Hello, Dr. Turr, I have the results of Ms. Evergreen's tests.

WENDY TURR: Are they conclusive?

DAVID FINKLE: Yes, I think we can diagnose Ms. Evergreen with acquired von Willebrand's disease. There is reduced activity of factor VIII (at 20%) and of ristocetin cofactor activity (at 14%), a low level of vWF (at 22%) and a loss of high-molecular-weight forms of vWF revealed on the multimer gel electrophoresis, which together confirm acquired **vWD.**

WENDY TURR: Let me have a look. Yes, you are correct. The normalization of the aPPT after adding normal plasma suggests that neither a factor VIII inhibitor, nor another inhibitor for that matter, is present. A factor VIII inhibitor would bind the factor VIII from the normal plasma and the aPTT would remain prolonged. Finally, ristocetin cofactor activity measures the functional ability of vWF to bind to platelets, so reduced activity is consistent with vWD. How is our patient's gingival bleeding?

DAVID FINKLE: It has **subsided**, but Ms. Evergreen is concerned that bleeding may **recur**.

WENDY TURR: Would you treat the patient or continue with further testing?

DAVID FINKLE: Well, I actually ordered further testing to understand what the **underlying** cause of the blood disorder was. I ordered a **bone marrow** biopsy, quantitative immunoglobulin assays and serum protein electrophoresis. You told me to come back to you before treatment and I have the results for these tests, too.

WENDY TURR: Good initiative. And have they allowed you to conclude on the underlying condition?

DAVID FINKLE: Given Ms. Evergreen's anemia, elevated level of serum **IgG** and **mildly** elevated creatinine level, I think **multiple myeloma** might be the cause. Testing revealed an IgG kappa monoclonal gammopathy, and there was more than 10% monoclonal plasma cells on examination of a bone-marrow biopsy specimen.

WENDY TURR: Good work, David. If there is, in response to the desmopressin-challenge test, an increase in a patient's level of von Willebrand factor antigen, factor VIII activity and restocetin cofactor activity, then desmopressin can be used to treat episodes of mild-to-moderate bleeding or can be used before procedures that may **precipitate** bleeding, such as dental work, to prevent excess bleeding. This can reassure your patient about future bleeding episodes.

*The patient was given a diagnosis of acquired von Willebrand's disease due to IgG multiple myeloma. She received chemotherapy with thalidomide and dexamethasone, and her IgG level, activated partial-thromboplastin time, factor VIII activity, level of vWF antigen, and ristocetin cofactor activity all returned to normal within 4 months. Thalidomide was prescribed as **maintenance therapy** but was subsequently **discontinued** because of side effects. Over the **ensuing** 2 years, Ms Evergreen had a slowly progressive increase in IgG levels but no apparent recurrence of acquired vWD. She underwent additional periodontal work without bleeding complications.*