Management of the Oral and Maxillofacial Surgery Patient With Thrombocytopenia

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Patients with disorders of coagulation and bleeding can be among the most challenging surgical patients to manage. Intraoperative or postoperative bleeding can contribute to life-threatening complications in even the most "benign" surgical procedures. An adequate number and function of platelets play a critical role in the coagulation pathway. A thorough understanding of platelet physiology and platelet disorders is therefore essential in the management of the thrombocytopathic oral and maxillofacial surgery patient. A careful preoperative evaluation will help the surgeon treat these patients and help prevent potentially catastrophic intraoperative or postoperative bleeding.
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Oral and maxillofacial surgeons are expected to treat patients with a wide spectrum of medical maladies. Patients with disorders of coagulation are among the most challenging patients to treat. Intra- or postoperative bleeding can contribute to life-threatening complications in even the most "benign" surgical procedures. Although the prevalence of bleeding disorders in patients being treated by dentists and oral and maxillofacial surgeons would appear to be small, 1 study showed that 2.3% of 1,500 adult dental school patients had bleeding problems and, indeed, bleeding disorders are more prevalent than cancer, renal disease, or joint replacement.[1] Hemostasis can be divided into 2 major components: coagulation and thrombosis. Successful hemostasis requires that both components work efficiently. The blood platelet plays a critical role in both components of the hemostatic system. Pathologic processes that significantly impair platelet function will have a devastating effect on the pro-

cesses involved in hemostasis. The purpose of this article is to discuss patients who have a platelet disorder and the factors relevant to their management.

Basic Platelet Physiology

Before discussing platelet disorders and their role in the management of the oral and maxillofacial surgery patient, it is important to review some basic principles of platelet production and function. When first viewed on peripheral blood smears, platelets were thought to be artifacts. It was not until 1882 that Bizzozero described platelet adhesiveness and the role of platelets in coagulation.[2] In 1910, the origin of platelets was finally discovered, and we now know that they are nonnucleated cell fragments that arise as buds from megakaryocytes, which differentiate in the bone marrow.[2,3] Like other hematopoietic cells, the megakaryocyte differentiates from pluripotent stem cells under the influence of growth and differentiation cytokines. Thrombopoietin, also called megakaryocyte growth and differentiation factor (MGDF) appears to be the most important of these hematopoietic cytokines.[4,5]

The platelets are initially in the marrow blood sinuses and then enter the general circulation. On average, there are approximately 2.5 to 3.0×10^8 platelets in each milliliter of blood, with normal platelet counts ranging from 150,000 to 400,000/μL. Approximately one third of the platelets released in the bone marrow are sequestered in the spleen. The remaining two thirds circulate in the blood, having a life span of approximately 7 to 10 days.[1-3]

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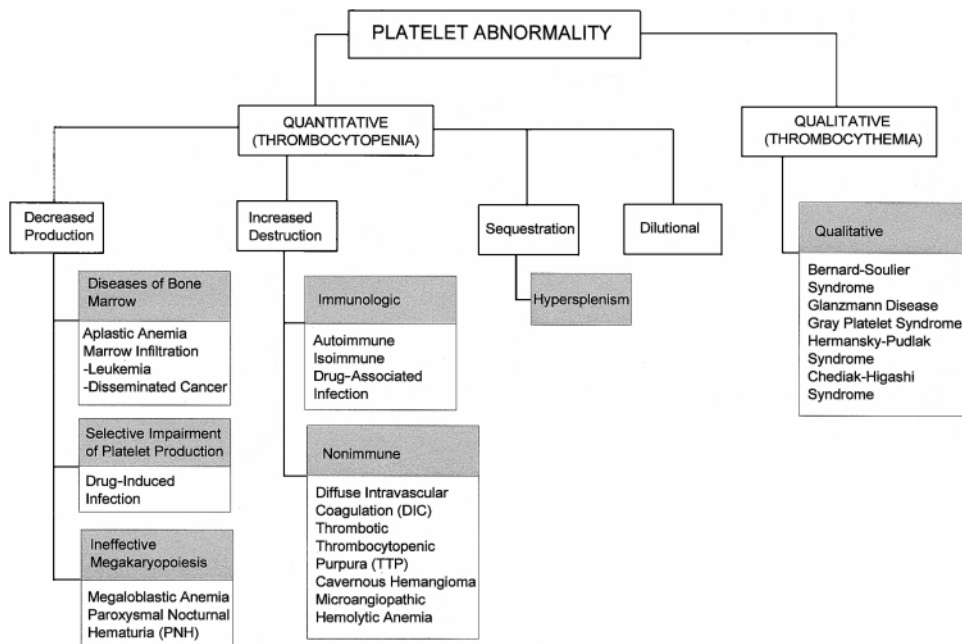
FIGURE 1. Causes of platelet abnormalities.

Platelets have a vital role in hemostasis and are said to have 4 main functions: 1) they help maintain the integrity of the capillaries; 2) they form the initial plug in vessel injury; 3) they elaborate various metabolically active substances such as serotonin, adenosine diphosphate (ADP), and platelet-factor III; and 4) they contain thrombasthenin—a contractile protein involved in clot retraction and consolidation of a fibrin plug.[2]

Platelet Disorders

Platelet disorders can be divided into 2 major categories: quantitative (too few, thrombocytopenia) and qualitative (dysfunction, thrombasthenia) (Fig 1). Thrombocytopenia is caused by 1 of 4 mechanisms: decreased production, increased destruction, sequestration, or dilution. Decreased platelet production is most frequently caused by marrow aplasia, marrow fibrosis, or infiltration of malignant cells into the bone marrow. Occasionally, myelosuppressive drugs (cytosine, arabinoside, daunorubicin, cyclophosphamide, and methotrexate) used to treat malignancies may lead to thrombocytopenia. Frequently, in these disorders, other components of the marrow are also suppressed, leading to anemia and granulocytopenia. Finally, several rare defects of thrombopoiesis are either caused by a lack of, or defects in, cytokines/hormones or their receptors required for development and proliferation of various hematopoietic components from pluripotent stem cells in the bone marrow (ie, thrombopoietin and erythropoietin).[2,3,5]

Thrombocytopenia is usually caused by increased destruction of platelets brought on by nonimmunologic and immunologic disorders. Nonimmunologic disorders include blood vessel disorders (vascular purpura), sepsis/disseminated intravascular coagulation (thrombocytopenic purpura), hemolytic uremic syndrome (HUS), thrombosis, and intravascular prostheses. Vascular purpura arises from damage to the endothelium of small vessels, abnormalities of the subendothelial matrix or perivascular connective tissues that support the blood vessels, or the formation of abnormal blood vessels. Thrombotic thrombocytopenic purpura (TTP) and HUS are closely related, idiopathic, fulminating, often lethal, disorders initiated by endothelial cell injury. These syndromes are characterized by thrombocytopenia, hemolytic anemia, fever, renal abnormalities, and neurologic disturbances. TTP is primarily a disease of adults, whose manifestations are primarily neurologic, whereas HUS is primarily a disease of children, where glomerular damage predominates. TTP appears to be caused by the presence in the plasma of large, multimeric, forms of von Willebrand Factor (vWF) (assumed to be released by damaged endothelial cells) and the lack of a specific metalloprotease to break it down. There appears to be both familial and acquired forms of TTP.[6,7] Factors that trigger endothelial cell injury include bacterial endotoxins, antibodies and immune complexes, oxidative injury, and certain drugs. HUS does not appear to be associated with the lack of the vWF protease or to autoantibodies, because most patients have normal protease activity. The pathophysiology of both the acquired and familial forms of HUS remains unknown.[7]

Immunologic disorders include drug-induced thrombocytopenias, viral and bacterial infections, acute

Table 1. COMMON DRUGS AFFECTING THE PLATELETS

Heparin
Aspirin
Ethanol
Thiazide diuretics
Antibiotics (eg, Sulfonamides, trimethoprimsulfamethoxazole)
Digoxin
Chemotherapeutic agents

idiopathic thrombocytopenic purpura (ITP), and chronic idiopathic thrombocytopenias caused by chronic autoimmune disorders (eg, systemic lupus erythematosis). Many drugs can cause thrombocytopenia (Table 1) by inducing an antibody response. Drug antibody complexes are formed, which activate complement and result in platelet destruction. Fortunately, most patients recover within 7 to 10 days after drug removal. A few patients may develop severe thrombocytopenia, with significant hemorrhage requiring immunosuppressive therapy and blood and platelet transfusions.[1-3,8,9]

Approximately 90% of acute ITP cases occur in children and occur after viral infections. Of these, 60% recover in 4 to 6 weeks and about 90% in 3 to 6 months. Acute ITP is caused by immune complexes containing viral antigens, which bind to platelet Fc receptors, or by antibodies produced against viral antigens that cross-react with epitopes of platelet adhesion molecules. Most patients with chronic ITP are adults, with women outnumbering men 3:1. These patients have autoimmune antibodies directed against various epitopes of platelet adhesion molecules (integrin alpha IIb, beta 3 [GP IIb, IIIa] or GP Ib-IX). These antibodies primarily act as opsonins that accelerate the phagocytic clearance of platelets. Some antibodies interfere with the function of these platelet adhesion molecules, preventing platelet activation.[3]

Normally, one-third of released platelets are sequestered in the spleen. Consequently, any condition that leads to splenic enlargement will increase the sequestration of platelets. The most common causes of splenomegaly are portal hypertension secondary to liver disease (alcoholic cirrhosis), splenic infiltration with tumor cells in myeloproliferative or lymphoproliferative disorders (leukemias and lymphomas), and storage disorders such as Gaucher disease.

The thrombasthenias are a group of relatively rare disorders that are caused by defects in platelet function. The best understood are defects in, or lack of, adhesion receptors required for platelet activation and aggregation such as Bernard-Soulier syndrome, which involves a defect in the GP Ib-IX complex required for binding to vWF, and Glanzmann disease, which is caused by a defect in, or deficiency of, the integrin alpha IIb, beta 3 (GP IIb, IIIa) required for fibrinogen binding. Both disorders are inherited as autosomal recessive traits. Recently, congenital defects in the platelet ADP receptor have been described, characterized by prolonged bleeding.[10]

Gray Platelet syndrome is a rare syndrome in which there is a defect in the storage of platelet secretory proteins in the alpha granules, which includes vWF, platelet factor 4, fibrinogen, thrombospondin, beta thromboglobulin, and platelet-derived growth factor—each of which plays a significant role in platelet aggregation.

Hermansky-Pudlak syndrome and Chédiak-Higashi syndrome are 2 related autosomal recessive syndromes characterized by defects in the synthesis or trafficking of lysosomal-related organelles, which include melanosomes, platelet dense granules, and lysosomes. Hermansky-Pudlak syndrome is characterized by oculocutaneous albinism, hemorrhage, and ceroid lipofuscin deposition leading to pulmonary fibrosis and obstructive pulmonary disease.[11] Chédiak-Higashi syndrome is characterized by variable degrees of oculocutaneous albinism, easy bruisability, bleeding, and recurrent infections. There is also a deficiency of platelet-dense granules, neutropenia, and abnormal NK cell function. The hallmark of the disease is the presence of huge, cytoplasmic peroxidase-positive, lysosome-like granules in granulocytes and other cells.[12] Platelet dense granules contain several coagonists in the process of platelet activation, which include ADP, epinephrine, and serotonin.

Patients with various forms of acute and chronic renal disease are also familiar to the oral and maxillofacial surgeon. Frequently, patients with uremia, or those on dialysis, exhibit coagulopathies. Although poorly understood, this bleeding tendency may be partly related to deficiencies in platelet aggregation and function caused by either deficiency or dysfunction of vWF or possibly vessel wall prostaglandins. Bleeding time is often elevated in these patients, and preoperative dialysis may need to be considered. Conjugated estrogens are particularly useful for these patients; however, they are not very effective for acute situations because of their long latency to achieve full effect.[13]

DIAGNOSIS

In general, an adequate medical history and physical examination will elucidate the oral and maxillofacial surgery patient with a platelet disorder. If the patient's history indicates one of the previously described diseases, it is important to further investigate the course and treatment of their disease, including consultation with their primary care provider or hematologist. Interpretation of clinical and laboratory
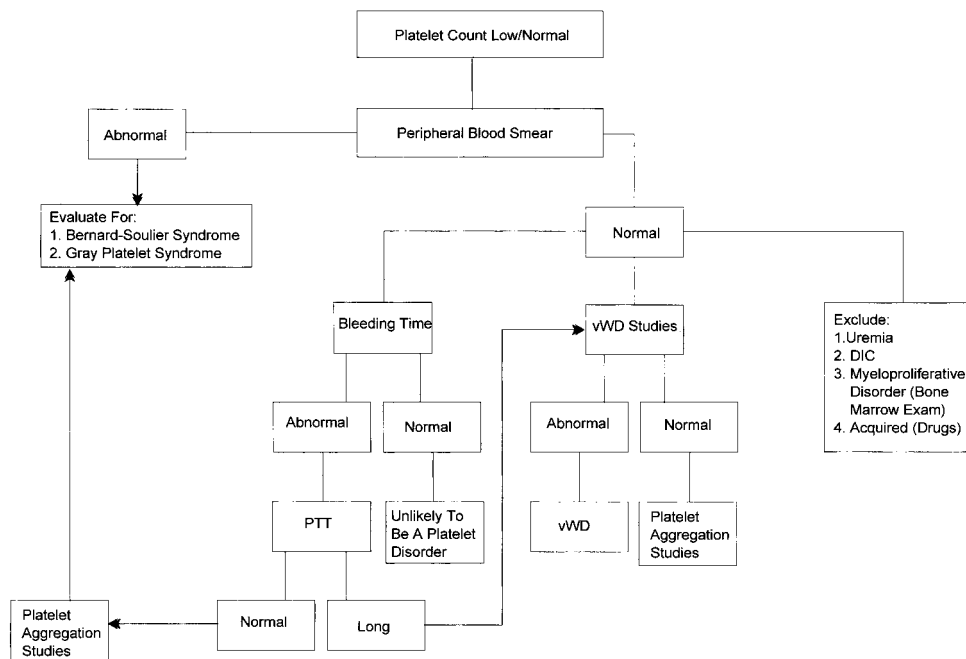
FIGURE 2. Algorithm for evaluation of platelet-type bleeding. (PTT, partial thromboplastin time; vWD, von Willebrand's disease; DIC, diffuse intravascular coagulation).

data should be made with knowledge of the patient's age, sex, race, current medications, and an assessment of general health.[14] This may prove to be essential, particularly with regard to evaluating current laboratory parameters and previous response to platelet transfusions.

In addition to a thorough history and physical examination, the following preoperative screening tests should be obtained (Fig 2): complete blood cell count (including platelet count), prothrombin time, partial thromboplastin time, fibrinogen level, and a bleeding time. A complete blood cell count is particularly important for determining if a thrombocytopenia is isolated or associated with anemia or leukopenia. Isolated thrombocytopenia may be the first sign of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome, occurring in as many as 11% of such patients. An HIV antibody test should be performed in patients whose history places them at risk.[1,9,15]

Bleeding time is another valuable test for evaluating patients with thrombocytopenia. In general, a linear relationship exists between the bleeding time and the platelet count when the platelet count is between 10,000 and 100,000/μL. This can be expressed as:

Bleeding time (minutes) =

$$30.5 - (\text{platelet count}/3,850)$$

A qualitative platelet defect should be suspected if the bleeding time is disproportional to the platelet count or if there is spontaneous bleeding with a platelet count of greater than 20,000/μL.[9] For patients known to be refractory to platelet transfusions, human leukocyte antigen (HLA) matching should be performed.

TREATMENT

Platelet transfusion should be considered in patients with thrombocytopenia or with altered platelet function who are actively bleeding or who are at risk of bleeding.[16] Because transfusion carries appreciable risk, the decision to prophylactically transfuse a patient before surgery is important. Although a platelet count of 100,000/μL is desirable for major surgery, minor surgery resulting in only superficial wounds can be performed with undue risk with platelet counts of 30,000 platelets per microliter.[14] Because of the relative inability to control hemorrhage in bony extraction sites by primarily closure, a platelet count of 100,000/μL is preferable, but not required. Lower values should be satisfactory in patients with uncomplicated histories. Other authors recommend a platelet count of 50,000/μL for minor procedures and 100,000/μL for surgery in critical areas or in the presence of hemorrhage.[17]

The number of platelet units to be transfused should be determined in a case-specific manner. Theoretically, the required number of units can be estimated according to the patient's body surface area or blood volume. However, most transfusions are administered empirically.[17] Pooled platelets may be appropriate for patients with uncomplicated histories. Patients with chronic platelet disorders have often had multiple previous transfusions and will be refractory to pooled platelet transfusions. The HLA antigens are primarily responsible for alloimmunization in the multiply transfused patient. After 10 to 15 transfusions of random donor platelets, most patients will be sensitized, and the life span of transfused platelets will be significantly shortened.[18] Although HLA identical sib-

lings provide the best matches, HLA identical random donors should be satisfactory. Advance arrangements with the local blood bank should be made ensure that matched platelets are available when necessary.

The timing of platelet transfusions, especially in multiply transfused patients, is essential. Ideally, a platelet count of at least 100,000/μL should be obtained on the morning of surgery in these patients. If matched platelets are unavailable, estimates regarding the required units of platelets required will mainly be a guess, based on the standard 5,000 to 8,000 increase in platelets per unit transfused. Patients with splenomegaly will quickly sequester platelets—matched or unmatched—which further emphasizes the need for preoperative planning. A posttransfusion platelet count should be obtained before surgery. Additional platelets can be transfused intraoperatively, if necessary, depending on the expected level of hemorrhage. Postsurgical transfusion secondary to sequestration during surgery may be required based on clinical criteria.

Surgical hemostasis is the first step in controlling bleeding in the thrombopathic patient. Local injection of a vasoconstrictor is also helpful. Dental extraction sites may be packed with Gelfoam (Pharmacia & Upjohn Co, Kalamazoo, MI) soaked in epsilon aminocaproic acid (EACA). EACA has been shown to inhibit the activity of fibrinolysins in saliva and therefore help preserve the clot.[14] Attempts should be made to provide primary mucosal closure of extraction sites with sutures. Bone bleeders should be addressed directly by bone burnishing, electrocautery, or application of bone wax before closing extraction sites. Gauze packs should be applied postoperatively. EACA may be used adjunctively on the packs.

Systemic pharmacologic management may be necessary if surgical hemostasis and platelet transfusion appear inadequate. Systemic EACA or tranexamic acid may be used. The antifibrinolytic action of these compounds is mainly related to their reversible complex with human plasminogen. Tranexamic acid is 7 to 10 times stronger than EACA and has a longer half-life. A loading dose of 10 g intravenous followed by 1 g/h is necessary to achieve an effective plasma concentration.[17] Desmopressin is a synthetic analog of arginine vasopressin that has been shown to prevent blood loss in patients with congenital and acquired platelet dysfunction. The recommended intravenous dose is 0.3 μg/kg. Intranasal desmopressin may be administered at 3 to 4 μg/kg.[17] A hematology consultation should be scheduled if one is unfamiliar with these drugs.

Complications of platelet and blood product transfusion should be reviewed preoperatively with patients. Common risks such as bacterial and viral infections and allergic reactions should be emphasized.

The patient should understand the risk of a reaction or infection per unit transfused: allergic or febrile reactions, 1:400; hepatitis C infection, 1:103,000; hepatitis B infection, 1:200,000; and HIV infection, 1:409,000.[19] Slower transfusion of blood products may prevent more serious allergic reactions. Prophylactic intravenous diphenhydramine may also help diminish allergic reactions. The reduction of white blood cells in transfusions is essential to limit febrile reactions. Consideration should also be made for viral diseases carried in white blood cells. A 10-fold reduction in white cell numbers before storage of platelets is sufficient to abolish most reactions.[16] Measures to ensure adequate leukoreduction should be made in chronically immunosuppressed patients such as organ transplantation patients and HIV-infected individuals.

The following case reports illustrate the management of patients with platelet disorders.

Case Reports

CASE 1

A 32-year-old African-American man was referred to the Oral and Maxillofacial Surgery Clinic at the University of Maryland for treatment of odontogenic pain. On examination, the patient was found to have abscessed upper right and left and lower left third molars. The remainder of the patient's dentition was in satisfactory condition. He was treatment planned for extraction of these teeth under general anesthesia. A medical history revealed an unknown platelet disorder, which had been diagnosed in childhood. He had received multiple blood product transfusions and was presumed to be infected with the hepatitis C virus. The patient's medical history was otherwise unremarkable. He had no allergies and was not taking prescription or over-the-counter medications.

Preoperative assessment of the patient included a complete history and physical examination, a complete blood cell count, a liver panel, and a chest radiograph. The patient was noted to have marked splenomegaly on physical examination. The preoperative complete blood cell count revealed white blood cells, 11.7×10^3/mm^3; red blood cells, 4.43×10^6/mm^3; hemoglobin, 11.8 mmol/L; mean corpuscular volume, 80.7 fL; and platelets 71,000/μL. The serum lactate dehydrogenase was markedly elevated at 2,900 U/mL, aspartate aminotransferase was 243 U/L, alanine aminotransferase was 66 U/L, and alkaline phosphatase was 92 U/L. A peripheral smear revealed that one third of the platelets were unusually large and hypogranulated. The bleeding profile revealed a partial thromboplastin time of 34 seconds, a prothrombin time of 13.5 seconds, a bleeding time of 13 minutes, a thrombin time of 15.2, and a normal fibrinogen level. The platelet reactive antibody panel was positive, with 29% reactivity and 18% positivity. The patient was HLA typed in the preoperative period.

A hematology consultation was obtained for his perioperative management. A review of the patient's medical record revealed a previously diagnosed, undefined platelet disorder in the granule deficiency family, similar to Gray Platelet syndrome. Because of the patient's alloimmunized status, preoperative platelet transfusion was performed to

augment the platelet count to at least 100,000/μL. The patient was admitted the day before surgery for platelet transfusions, and received 18 units of non-HLA matched platelets the morning of surgery. The posttransfusion platelet count was 67,000/μL, and the patient was cleared for surgery by the hematology department. An additional 6 U of non-HLA matched platelets were infused perioperatively. The patient was taken to the operating room, and the previously mentioned teeth were extracted under general anesthesia. Gelfoam was packed into the extraction sites, and primary closure with 3-0 chromic suture was achieved. Pressure was maintained with gauze packs. The patient was extubated and returned to the recovery room without complication. The postoperative platelet count was 76,000/μL. The patient continued to ooze blood from the extraction sites, and a final transfusion of 6 U of HLA-matched platelets was infused when the patient returned to the ward. Adequate hemostasis was achieved by the evening of surgery. He did well in the postoperative period, and no recurrence of bleeding was noted. The patient was observed for 1 day postoperatively and discharged with instructions for follow-up. An examination at 1 week revealed granulating extraction sites, with no bleeding episodes reported.

CASE 2

A 31-year-old African-American man was referred to the Oral and Maxillofacial Surgery Clinic at the University of Maryland for extraction of multiple, nonrestorable, carious teeth. A review of the past medical history revealed insulin-dependent diabetes, intravenous drug abuse, HIV with a CD4 too low to count, pancytopenia, and recent fevers of unknown origin. The patient was treatment planned to have multiple extractions using local anesthetic after preoperative transfusion of platelets and fresh-frozen plasma. Medications included dapsone, lansoprazole, fluconazole, and NPH insulin. The patient had no known drug allergies. Preoperative assessment included a complete history and physical examination, a complete blood cell count, a liver panel, and chest radiograph. The preoperative platelet count was 50,000/μL. The patient was transfused with 8 U of platelets the morning of surgery. The post-transfusion platelet count was 125,000/μL.

Extraction of the teeth was performed under local anesthesia in the oral and maxillofacial surgery outpatient clinic. The surgical sites were closed primarily and adequate hemostasis was observed. On postoperative day 1, a slight ooze was noted from the patient's extraction sites. However, no intervention was required at that time. On postoperative day 2, frank bleeding was observed from the extraction sites, despite an intact primary mucosal closure. The patient was admitted to the hospital for evaluation and to control his thrombocytopenia. He subsequently was transfused with 6 U of platelets on the day of admission. However, the patient became unstable and was transferred to the intensive care unit. In the intensive care unit, the patient received multiple transfusions of packed red blood cells and platelets, with a transient response. Thrombin-soaked gauze was placed locally over the surgical sites as an adjunctive measure for hemostasis. The hematology department, who followed the patient on an outpatient basis, was consulted and they believed that the thrombocytopenia was likely related to his HIV disease, because it had improved moderately on antiviral treatment in the past. They rejected ITP as a cause because of hypoplasia seen on a recent bone biopsy. The patient achieved complete hemostasis

and was transferred back to the medicine floor where he was later discharged.

CASE 3

A 39-year-old African-American woman was referred to the Oral and Maxillofacial Surgery Clinic at the University of Maryland for evaluation of multiple, nonrestorable, carious teeth. The patient was treatment planned for full-mouth extraction and alveoloplasty with primary closure. On examination, the patient had generalized severe caries. Review of the past medical history revealed HIV with a CD4 count of 456, end-stage liver disease secondary to hepatitis C, portal hypertension, and a coagulopathy. Medications included dapsone, didanosine, abacavir, efavirenz, and furosemide. The patient had allergies to trimethoprim/sulfamethoxazole and ibuprofen. Preoperative assessment included a complete history and physical examination, complete blood cell count, a coagulation/liver panel, electrolytes, and a chest radiograph.

The patient was admitted to the hospital, and a complete blood cell count and coagulation panel were obtained just before the procedure. The significant values included a white blood cell count of $5.2 \times 10^3/\text{mm}^3$, a hematocrit of 30.9%, a platelet count of $58 \times 10^3/\mu\text{L}$, and an INR of 2.3. The patient received 7 U of platelets and 2 U of fresh-frozen plasma preoperatively and an additional 2 U of fresh-frozen plasma during the procedure. The procedure was completed without complications, and primary closure was obtained with good hemostasis. Postoperatively the patient received an additional 2 U of plasma in the recovery unit, and was transferred to the floor. Hemostasis was maintained throughout her hospital course. Of significance, postoperatively, she developed severe angioedema periorally, which resolved within 3 weeks after discharge.

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