

# Management of Tooth Extraction in a Patient With a Rare Bleeding Disorder Associated With Hermansky-Pudlak Syndrome: A Case Report

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**Purpose:** This report describes the case of a 27-year-old man who had been diagnosed with Hermansky-Pudlak syndrome shortly after birth. Because the patient had a major bleeding disorder associated with his syndrome, local and systemic hemostatic protection recommendations had to be considered before tooth extraction.

**Materials and Methods:** Synthetic vasopressin (1-deamino-8-d-arginine vasopressin [DDAVP]) was transfused intravenously before surgery. During surgery the patient was transfused with 1 U of human leukocyte antigen (HLA)-matched apheresis platelets. A hemostatic packing of Avitene and Gelfoam was adapted to the extraction site.

**Results:** Treatment with DDAVP, HLA-matched platelets, and local application of a packing with Avitene and Gelfoam resulted in sustained hemostasis and an excellent healing response.

**Conclusion:** Surgical and routine extractions appear to be safe procedures in patients with Hermansky-Pudlak syndrome when appropriate local and systemic hemostatic measures are used.

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Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by oculocutaneous albinism (OCA), increased bleeding tendency, and ceroid storage abnormalities. It was first described by 2 Czech internists, Frantisek Hermansky and Paulus Pudlak, in 1959.<sup>1</sup> They recounted the cases of 2 unrelated patients with albinism and markedly prolonged bleeding times, nystagmus, and large pigmented reticular cells in their bone marrows. These classic findings result from defects of multiple cytoplasmic organelles: melanosomes, platelet-dense granules, and lysosomes. Varying amounts of skin melanin and associated albinism are seen based on severity. Ocular symptoms also arise from defective melanosomes and often manifest as photophobia, strabismus, nystagmus, and vision acuity impairment. Individuals with the syn-

drome have major platelet dysfunction and tend to bruise and bleed easily. The cellular storage disorder results in a ceroid accumulation in the body tissues and causes damage, especially in the lungs and kidneys.<sup>2</sup> Ceroid deposition in patients with HPS has been associated with pulmonary fibrosis, granulomatous enteropathic disease, and renal failure.

The bleeding diathesis of HPS results from absent or severely deficient dense granules in platelets.<sup>3</sup> Several important chemicals (adenosine diphosphate [ADP], adenosine triphosphate [ATP], serotonin, calcium, and phosphate) related to hemostasis are normally stored in these dense granules. When an injury, such as a cut, occurs, platelets normally release the contents of their dense granules. ADP attracts surrounding platelets and they become “activated” and change

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their shape to become stellate. Platelets become “sticky” and aggregate on the wall of a damaged blood vessel. In HPS, platelets are not attracted to each other and do not change shape or become activated. The ATP contained in the dense granules of normal platelets is necessary for the production of threads of fibrin in the blood. Fibrin acts like a net that traps red blood cells and platelets. Together they form a blood clot at the site of injury. In HPS, fibrin threads do not form a strong net. Clots are slow to form, and when they eventually form, they are unstable and degrade easily.<sup>4</sup>

The synthetic analog of the antidiuretic hormone vasopressin (1-deamino-8-d-arginine vasopressin [DDAVP]) has been used successfully for the management of platelet function defects. DDAVP is an appealing hemostatic adjunct for several reasons. DDAVP is inexpensive, especially compared with coagulation factor concentrates. It also involves no risk of transmission of viruses or new pathogens, and it prevents exposure to coagulation factors or platelet concentrates, decreasing the risk of immunization.<sup>5</sup>

Platelet transfusion is a standard part of therapy for different patients with thrombocytopenia or platelet dysfunction. Platelets are processed, tested, and labeled in a manner similar to that for whole blood, which includes ABO and Rh typing and required testing for transfusion-transmitted diseases.<sup>6</sup> Platelets can be administered intraoperatively to maximize circulating platelets available for hemostasis at the time of surgery.

## Report of Case

This report describes the case of a 27-year-old man (Fig 1) who was diagnosed with HPS shortly after birth. He underwent subsequent genetic studies at the National Institutes of Health, where he is a participant in the Natural History of Hermansky-Pudlak Syndrome study.

The patient exhibited 2 classic clinical manifestations of HPS, OCA and a bleeding diathesis. The patient reported a history of bleeding with seemingly trivial abrasions, such as excoriation of his acne. He denied spontaneous oral mucosal bleeding, but reported occasional epistaxis during the winter months. Review of the gastrointestinal system was negative for evidence of colitis, and he exhibited no signs of pulmonary fibrosis.

Blood was tested for type and screen, coagulation profile, complete blood cell count, and complete metabolic profile (Table 1). Several hematologic studies also were performed. This included a DDAVP bleeding time challenge, which showed objective qualitative changes, but failed to show improvement of bleeding time. However, there was an excellent increase in von Willebrand factor (vWF) assays after DDAVP infusion; hence, this medication was considered a useful adjunctive hemostatic measure.



**FIGURE 1.** Photograph of patient with Hermansky-Pudlak syndrome.

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A panoramic radiograph was obtained and reviewed (Fig 2). The mandibular right second molar showed radiographic evidence of failing endodontic therapy and was deemed non-restorable by the patient’s general dentist.

## Materials and Methods

DDAVP 0.3  $\mu\text{g}/\text{kg}$  (20  $\mu\text{g}$  in 5% dextrose 50 mL) was transfused intravenously over 45 minutes, 1 hour before surgery. During surgery the patient was transfused with 1 U of human leukocyte antigen (HLA)-matched apheresis platelets over 30 minutes.

Local anesthesia was administered in a standard block and infiltrative manner using 3 cartridges (5.4 mL) of 2% lidocaine with 1:100,000 epinephrine. The mandibular right second molar was extracted without complication or damage of gingival soft tissue. A hemostatic packing (Avitene (Davol, Inc. Warwick, RI) and Gelfoam (Pfizer Inc, New York, NY)) was adapted to the extraction socket and secured with a 4-0 silk suture.

The patient was monitored in the clinic for 1 hour before being transported back to his hospital room.

**Table 1. TESTING FOR PATIENT WITH HERMANSKY-PUDLAK SYNDROME**

Blood type	B
Screen	Rh <sup>+</sup>
Coagulation profile	
PT (seconds)	14.1
INR	1.1
PTT (seconds)	36.7
Hematology	
WBC count (thousands/ $\mu$ L)	5.2
Hemoglobin (g/dL)	16.2
Hematocrit (%)	46.1
Platelet count (thousands/ $\mu$ L)	220
Complete cell count	
Sodium (mmol/L)	139
Potassium (mmol/L)	4.7
Chloride (mmol/L)	102
CO <sub>2</sub> (mmol/L)	29
Urea nitrogen (mg/dL)	14
Creatinine (mg/dL)	0.90
Glucose (mg/dL)	83

Abbreviations: INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell.

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The platelet transfusion was completed without complication. The patient received a second planned 20- $\mu$ g DDAVP infusion 6 hours from application of local hemostatic agents.

## Results

The patient was admitted for 24-hour observation. No significant bleeding was encountered during admission, with an estimated blood loss of less than 10 mL. There were no adverse reactions from the platelet and DDAVP infusions. No important change was noted to patient's metabolic profile. The patient showed normal healing at the time of suture removal, 4 days postoperatively. Two-week follow-up showed excellent healing at the extraction site. The patient did not require pain medication.

## Discussion

Management of patients with HPS requiring tooth extraction involves close cooperation between the hematologist and the oral and maxillofacial surgeon. The hematologist should be consulted to characterize the patient's bleeding risk and to determine an appropriate prophylactic regimen to prevent secondary local bleeding during oral interventions. Standard blood tests, such as prothrombin time, partial thromboplastin time, and platelet count, usually do not iden-

tify the platelet defect in HPS.<sup>7</sup> The amount of prolonged bleeding varies in affected individuals from very mild to life threatening. A period of in-house observation is prudent because seemingly trivial bleeds can be life threatening. Careful follow-up after discharge also is vital to observe for delayed bleeding. Fatal bleeding after tooth extraction has been reported in these patients.<sup>8</sup>

DDAVP affects hemostasis by increasing the plasma levels of factor VIII, vWF, and platelet adhesiveness while having no effect on platelet count.<sup>9</sup> DDAVP shortens the prolonged activated partial thromboplastin time and the bleeding time.

General recommendations on patient management with DDAVP are well documented.<sup>10</sup> A single intravenous dose of 0.3  $\mu$ g/kg body weight is usually diluted in at least 50 to 100 mL of physiologic saline and given by slow intravenous infusion over 30 minutes. One of the immediate effects of DDAVP is a facial flushing-type reaction, which is not particularly dangerous, but a general nuisance. The present patient had this flushing reaction at prior challenges with DDAVP; thus, the decision was made to draw out the infusion to 45 minutes from the standard 30 minutes and to premedicate with diphenhydramine. The peak response is seen approximately 60 minutes after intravenous or subcutaneous administration. The necessity for repeat administration of DDAVP for hemostasis should be determined by laboratory response and the clinical condition of the patient. The tendency toward tachyphylaxis with repeated administration given more frequently than every 48 hours should be considered when treating each patient.

When administering DDAVP, fluid intake should be adjusted downward to decrease the potential occurrence of water intoxication and hyponatremia with accompanying signs and symptoms, including headache, nausea, and vomiting. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures, which could lead to coma. DDAVP acetate should not be used to treat patients with type IIB von Willebrand disease because platelet aggregation can be induced.<sup>11</sup>

In the present case, a transfusion of  $4.25 \times 10^{11}$  HLA-matched platelets was administered intraoperatively to maximize circulating platelets available for hemostasis at the time of surgery. HLA typing was performed for the purpose of administering matched products to stave off platelet refractoriness. Also, because pulmonary fibrosis typically supervenes and alloimmunization is a great concern (should lung transplantation be requisite), the decision was made to supply perfectly matched platelets; hence, the administration of HLA-matched platelets in this case.

There is a dose-response effect from platelet transfusion. Within 1 hour after transfusion, the platelet



**FIGURE 2.** Panoramic radiograph of the mandibular right second molar shows evidence of failing endodontic therapy.

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count increases approximately 10,000/ $\mu\text{L}$  when  $1 \times 10^{11}$  platelets are transfused into a typical 70-kg patient. The usual dose of approximately 3.5 to  $4.0 \times 10^{11}$  platelets causes the platelet count to increase by 35,000 to 40,000/ $\mu\text{L}$  in an average-sized adult.

A packing consisting of Avitene and Gelfoam was adapted to the extraction site as a local hemostatic measure. Avitene is an absorbable hemostatic agent prepared from purified bovine corium collagen and shredded into fibrils to increase surface area. When in contact with a bleeding surface, Avitene attracts platelets that adhere to its fibrils and undergo the release phenomenon. This triggers aggregation of the platelets into thrombi in the interstices of the fibrous mass, initiating the formation of a physiologic platelet plug.<sup>12</sup>

The Gelfoam sterile compressed sponge is a water-insoluble hemostatic device prepared from purified porcine skin gelatin and capable of absorbing up to 45 times its weight of whole blood.<sup>13</sup> The clotting effect of Gelfoam results from thromboplastin release from platelets, occurring when platelets entering the sponge become damaged by contact with the walls of its myriad of interstices. The spongy physical properties of the gelatin sponge hasten clot formation and provide structural support for the forming clot.

The patient had no drug allergies, but aspirin and nonsteroidal anti-inflammatory drugs are absolutely contraindicated owing to bleeding risks. Acetaminophen is the analgesic of choice in patients with HPS.

Prior bronchoscopy showed no evidence of pulmonary fibrosis. Typically symptoms appear in the early 30s and can progress to death within a decade.<sup>14</sup> Pulmonary function may decline in advance of lung findings at imaging; thus, intravenous sedation may be a risky proposition for those with HPS.

Treatment with DDAVP, HLA-matched platelets, and packing with Gelfoam and Avitene resulted in sustained hemostasis and an excellent healing response. In conclusion, surgical and routine extractions appear to be safe procedures in patients with HPS when

appropriate local and systemic hemostatic measures are used.

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