Gingival response to G-CSF in a patient with congenital agranulocytosis: case report

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Introduction

Neutropenia is a quantitative blood disorder characterized by a decrease in the number of polymorphonuclear leukocytes. The peripheral blood level of neutrophils reaches a level of less than 1500 cells per microliter.[1] The extent of neutropenia is variable and differs with the age and race of the patient. In cyclic neutropenia, there are episodes in which the total neutrophil count oscillates from an acceptable level (i.e., > 1500 per microliter of blood), to a neutropenic level (i.e., < 1500 per microliter). As the degree of neutropenia increases, a concomitant increase in the severity of infection may develop.[2] There also may be an associated monocytosis, in addition to the neutropenic episodes, which last an average of 14–21 days.[3, 4] In the congenital form, first described by Kostmann in 1956, children are born with less than 200 neutrophils/ml, and this level remains low.[3] Kostmann stated that for the particular geographic region the incidence of infantile genetic agranulocytosis was 1 in 674.[5] This disease appears to be autosomal recessive, since only isolated cases have been reported.[3, 6] Bone marrow aspiration shows a maturation arrest at the promyelocyte or myelocyte stage.[1, 4]

Patients with congenital neutropenia may have an increase in the number of lymphocytes, may convert to a myelogenous leukemia, and are susceptible to life-threatening infections.[4] Clinical manifestations of the disease may not be evident until patients develop bacterial infections. These usually are caused by *Staphylococcus aureus* or *Escherichia coli*, and occur in such sites as the urinary tract, lungs, ears, and oral cavity.[7] Both forms of agranulocytosis are characterized intraorally by ulcerations of the oral mucosa and a granulomatous form of marginal gingivitis. Prognosis in the congenital disease is guarded, and conventional treatment may include prophylactic antibiotics, steroid therapy, splenectomy, and bone marrow transplantation. Recent advances in medical management, including the use of granulocyte colony stimulating factor (G-CSF),[4, 8, 9] have resulted in fewer systemic infections and markedly reduced marginal gingivitis. G-CSF is a specific glycoprotein that functions as a hematopoietic growth factor to control granulocyte and monocyte populations in the blood.[9, 10] The gene for human G-CSF has been cloned, resulting in the availability of the recombinant form of G-CSF which is used to treat congenital agranulocytosis.

Oral manifestations of congenital agranulocytosis include gingivitis — ranging from mild to severe; necrotizing ulcerations of the mucosa, lips, tongue, pharynx, and tonsillar areas; and increased salivary flow. In its most severe form, patients experience spontaneous oral bleeding, severe pain, and an inability to eat. Prophylactic or therapeutic antibiotics may help, but meticulous oral hygiene is the best method of preventing oral infection. During acute exacerbations, patients may rinse with a combination of diphenhydramine hydrochloride and kaolin/pectin (Benadryl®/Kaopectate® as a 50:50 mixture) prior to meals in order to alleviate some of the pain associated with the oral ulcerations, and use chlorhexidene rinses twice daily to minimize plaque buildup.

Case report

J. S. is a white female who presented at the age of 8 years, 8 months for consultation and management of ulcerations on the lips, tongue, and gingivae. The patient was well known to this hospital previously having been admitted for a finger infection, fever with malaise, oral ulcerations, lymphadenopathy, and comprehensive restorative dental treatment under general anesthesia. J. S. was the product of a full-term pregnancy and Caesarean birth, and was the only child to be born to her parents. There was no previous familial history of agranulocytosis. The maternal history was negative for teratogenic drugs, alcohol use, or smoking. The patient was diagnosed as having congenital agranulocytosis at age 8 weeks when she developed abdominal wall cellulitis and omphalitis. She had recurrent lymphadenopathy and infections of the lips, tongue, and gingivae requiring admission to the hospital for treatment. Typically, her PMN count ranges from 0 to 300/mm^3. Diagnosis has been confirmed by bone marrow aspiration, which showed a mildly hypercellular marrow with a myeloid shift to the left, as well as decreased maturation of the myeloid cells. She routinely takes trimethoprim/sulfamethoxazole (Bactrim™), 150 mg po bid, for prophylaxis.

On admission, the patient had an elevated body temperature of 39.6° C, and the concern was to prevent a severe systemic infection. J. S. was afebrile when seen in dentistry (one day after admission), but the cbc with differential indicated that neutrophils were 3% (normal 40–70%), lymphocytes 70% (normal 25–45%), and monocytes 18% (normal 1–8%). She was being treated with amoxicillin/clavulanate potassium (Augmentin®), 250 mg po q8h, and ampicillin/sulbactam (Unasyn®), 1.7 g q6h IV,

for lymphadenitis and oral ulcerations.

Oral examination revealed multiple ulcerations on the gingivae, oral mucosa, and lips. The lips were heavily encrusted and oral opening was restricted. The marginal gingiva was deep blue-red, friable, had areas of granulomatous hyperplasia, and cratering of the papillary gingiva. There was a general distribution of heavy materia alba on the teeth, but no obvious carious lesions. A generalized enamel hypoplasia was observed throughout the dentition, which might reflect severe metabolic disturbances from infection during dental development. The dentition was age appropriate. Radiographs revealed lower than normal bone height for her age and several deep radiolucent bony defects. J. S. complained that she was unable to brush or eat due to pain and bleeding. She was placed on chlor-hexidene (Peridex®) rinses twice daily, and Benadryl®/Kaopectate® rinses prior to meals. She was scheduled for light prophylaxis as her blood counts improved, and efforts were made to instruct her and the hospital nursing staff in appropriate oral hygiene techniques (i.e., rinses and brushing with Toothettes® or toothbrush). J. S. was discharged to her parents on the sixth day, afebrile and with resolving oral lesions and scheduled for routine out-patient dental follow-up.

One month later, J. S., now 8 years, 9 months old, presented to the emergency room with fever, oral ulcerations, and cervical lymphadenitis and was admitted (sixth admission) for treatment, as well as for the initiation of G-CSF therapy.

The course of treatment included intravenous infusion of ampicillin/sulbactam (Unasyn®), 1.5 g q6h IV subcutaneous injection of G-CSF at a rate of 5 micrograms/kilogram daily; and meticulous oral hygiene including chlorhexidene (Peridex®) rinses. Progress was monitored daily via cbc with differential cell counts.

Within four days of admission, the oral ulcers, fever, and lymphadenitis resolved. On the fifth day the cbc revealed a neutrophil count of 5%, up from, admission count of 0%, and the patient was discharged on trimethoprim/sulfamethoxazole (Bactrim™ 160 mg bid, po), penicillin (250 mg qid, po), and G-CSF (175 micrograms daily, subcutaneously). Three weeks later, gingival health was remarkably improved, with markedly reduced swelling and redness at the gingival margins. J.S. reported a significant decrease in discomfort when brushing her teeth, allowing more effective removal of plaque and food debris. As at every visit, home care instructions were reviewed, and the patient was placed on a three-month recall schedule.

Discussion

The patient's diagnosis of generalized prepubertal periodontitis (PP) was made based on established criteria.[11, 12] These included the clinical findings of generalized attachment loss and moderate to severe diffuse gingival inflammation, and radiographic evidence of alveolar bone loss at multiple interproximal and furcation sites. The prognosis for the involved primary dentition was considered to be poor, with likely progression to full involvement of the permanent dentition in view of the inadequate neutrophil count.

The goal of periodontal therapy, as well as chlorhexidene rinses as part of the home care regimen, was to reduce the risk of periodontal infection as a source of septicemia. In fact, over a two-year period, the only intraoral sources of systemic infection noted appeared to be secondary to local infection following accidental trauma to the tongue or buccal mucosa.

The dramatic improvement in the health of the oral soft tissues following initiation of G-CSF therapy correlated with the G-CSF-induced increase in circulating neutrophils. While the etiologic basis of PP in this case was likely based on a severe quantitative decrease in circulating neutrophils, etiology in other PP cases may be based instead on certain qualitative deficits in neutrophil function,[13] which may not be amenable to treatment with currently available pharmacological agents.

Gingival inflammation and periodontal infection occurs in many children, but it is of particular concern in immunocompromised patients. Congenital agranulocytosis results in a severely depleted reservoir of neutrophils from birth. As a result, any infection, oral or systemic, may have serious consequences. A curious form of granulomatous gingivitis is seen in these patients, further complicated by an unwillingness or inability to maintain adequate oral hygiene. G-CSF has been shown to increase the number of circulating mature neutrophils and, in turn, to improve oral soft tissue health. In J. S., while there was an increase in the peripheral neutrophil count, it was not clear whether all of the mature cells were fully functional. As previously reported,[9] a significant decrease in gingival inflammation and in the frequency of recurring oral lesions occurs following G-CSF therapy. This improvement in oral soft tissue and gingival health has allowed more effective home care and an improved attitude toward meticulous maintenance of oral hygiene.

With restitution of adequate numbers of neutrophils following successful treatment with G-CSF in this case, the periodontal prognosis is dramatically improved. It now becomes much less likely that the already involved primary dentition will experience continuing loss of both attachment and alveolar bone. Furthermore, the prognosis for the periodontal health of the permanent dentition is likely to be very good in the presence of continued excellent home care and the success of G-CSF therapy.

Inasmuch as this relatively new pharmacologic treatment modality for congenital agranulocytosis is effective, it is important to realize that maintenance of sound oral hygiene remains the foundation for preventing future oral infections. Antibacterial rinses (e.g. Peridex®) may serve as adjuncts in reducing plaque and local irritation, and any resulting stain may be temporarily acceptable. Oral hygiene instruction and periodontal maintenance must begin early, and may include both mechanical and chemical means of plaque control to complement pharm-

acologic treatment. By reducing the oral manifestations of this systemic disease, G-CSF promises to improve oral hygiene and further prevent complications of the disease.

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