Clinical Pathologic Conference Case 5: Agranulocytosis

Z. B. Kurago · A. R. Kerr · N. Narayana

Received: 27 June 2011 / Accepted: 19 August 2011 / Published online: 31 August 2011
© Springer Science+Business Media, LLC 2011

Clinical Presentation

A 28-year-old thin male presented as an outpatient to the New York University Langone Medical Center complaining of a painful “blister” on his tongue of approximately 8 days duration, preceded by a fever. The pain caused difficulty speaking, but had no effect on swallowing, and the patient controlled the pain intermittently with ibuprofen. The patient did not recall recent trauma to the tongue. He was treated by his physician with levofloxacin, famciclovir, a sucralfate rinse, and a probiotic containing *Saccharomyces boulardii* lyo, and felt some improvement. The patient also reported a history of occasional small aphthous ulcers, which always resolved quickly.

The patient’s medical history included sinus infections approximately once per year, which had been managed with clindamycin because of his hypersensitivity to penicillin and amoxicillin. The most recent sinus infection and treatment with clindamycin occurred 1–2 weeks prior to the onset of the current illness. For the preceding year and a half, the patient had been having intermittent abdominal discomfort, recently including diarrhea, for which the evaluation was still in progress. Except for low blood pressure, the patient denied other organ and system disorders.

Extraoral examination of the head and neck area revealed no abnormalities. Intraorally, there was a 2 cm

tender raised ulcer with thick fibrin, induration, and surrounding erythema on the left anterior dorsal surface of the tongue (Fig. 1a). With the exception of dental restorations, no other abnormalities were identified during the head and neck examination.

Clinical Differential Diagnosis

The clinical presentation suggested possibilities ranging from infection to neoplasia. Among non-infectious, non-neoplastic disorders, traumatic ulcerative granuloma was at the top of the differential diagnosis due to its location on the dorsal surface of the tongue, the large size, and pain and induration of the ulcer, although this lesion would not explain the fever. Infections associated with granulomatous inflammation were also high on the differential due to the large size and induration of the ulcer. Infections more likely to present this way include deep fungal infections and selected bacterial infections (Table 1), while protozoal infections are rare. These infections typically also present with lymphadenopathy, which was not evident in the current case. Neoplasia was less likely given the rapid onset and the associated fever, although high-grade lymphoma could not be excluded (Table 1). While the fever could be unrelated to the ulcer, this was less likely given the close chronologic proximity of the two signs (fever followed by ulcer).

Traumatic ulcerative granuloma is a relatively common lesion that presents as a deep, indurated and painful ulcer of unknown cause, most often seen in the tongue. In distinction from other ulcers, traumatic ulcerative granuloma is characterized by the extension of tissue damage into the skeletal muscle with mixed inflammatory infiltrates that include eosinophils [1, 2].

Z. B. Kurago (✉) · A. R. Kerr
Oral and Maxillofacial Pathology, Radiology and Medicine,
NYU College of Dentistry, New York, NY, USA
e-mail: zk8@nyu.edu

N. Narayana
UNMC, College of Dentistry, Lincoln, NE, USA

◀ **Fig. 1** Initial presentation of the tongue lesion. **a** Clinical image of the tongue. Note the thick surface fibrin creating a dome-like elevation. **b** Histopathologic features of the tongue lesion (H&E). *Top*: Low power image (4× objective) showing the ulcer surface with thick fibrin and bacteria and the underlying ulcer bed with dense inflammatory infiltrates. *Middle*: Medium power image (20× objective) of the mononuclear inflammatory infiltrate. *Bottom*: Medium (20× objective) and high power (40× objective) images of the deep portion of the lesion showing extension of the mononuclear inflammatory infiltrate and eosinophils into skeletal muscle with degeneration of muscle fibers

[1, 4]. Increasingly, atypical and drug-resistant forms are seen, often associated with immunocompromised states, such as HIV/AIDS [1].

Histoplasmosis and blastomycosis are the two more common deep fungal infections caused most frequently by *Histoplasma capsulatum* and *Blastomyces dermatitidis*, respectively, that can affect the oral cavity [1]. Similar to TB, oral lesions primarily manifest with systemic infections, usually as indurated ulcers with granulomatous inflammation [1]. Various immunocompromised states, such as HIV/AIDS, predispose to such infections [1].

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*, which induces granulomatous inflammation [1, 5]. The oral cavity is the most common extragenital site [5]. Among the various stages of this infection, the primary lesion is typically a single indurated ulcer (chancre), which is compatible with the clinical presentation in this case. Primary syphilis presentation in the tongue in HIV/AIDS has been described [6].

Non-Hodgkin lymphoma, more likely of diffuse large B cell type, in the oral cavity, primarily presents in lymphoid tissue-rich areas and in bone, while the anterior tongue is an uncommon site [7, 8]. Typical presentation is a soft tissue enlargement with or without ulceration [1, 9]. Fever is not characteristic of this condition, except in advanced cases [3]. Rarely, other non-Hodgkin lymphomas have been described in the tongue.

Immunocompromised states not only predispose to many infections and to infection-induced neoplasia, but also affect the clinical presentation of infections, often leading to more aggressive and destructive lesions with so-called atypical features. Considering the patient's age and recent onset of the lesion, and lack of evidence for increased susceptibility to infections in the preceding 27 years of his life, only acquired immunodeficiencies are in the differential diagnosis. Among these, HIV/AIDS and reductions in leukocytes, especially neutrophils, are the most likely.

HIV/AIDS is caused by the human immunodeficiency virus, leading to profound immunosuppression. In the oral cavity, the AIDS-associated infections listed above and non-Hodgkin lymphoma (particularly EBV-associated lymphoma), are known to present similar to the case at hand. Moreover, ulcers caused by HSV and CMV can

Tuberculosis (TB) is caused by several strains of an intracellular bacillus, usually *Mycobacterium tuberculosis*, resulting in granulomatous inflammation [3]. In the oral cavity, a large, indurated ulcer is the usual presenting sign

Table 1 Differential diagnosis

Group of conditions	More likely specific conditions	Diagnostic procedures
Ulcers of unknown cause	Traumatic ulcerative granuloma	Biopsy + CBC with differential
Infections with ulceration and granulomatous inflammation	Histoplasmosis, blastomycosis, tuberculosis, syphilis, other less common infections	Biopsy + CBC with differential; lab tests as needed for specific infections
Neoplasms	Non-Hodgkin lymphoma; others (e.g. Langerhans cell histiocytosis)	Biopsy
Acquired immunocompromised states	HIV/AIDS (predisposing condition to infections or lymphoma included above), as well as viral infections: HSV, CMV	Biopsy + CBC with differential + HIV test; other lab tests as needed for specific infections
	Neutropenia or agranulocytosis	Biopsy + CBC with differential + bone marrow biopsy

present on the dorsal surface of the tongue and are particularly destructive in immunocompromised hosts, such as AIDS patients. Superimposition of HSV and CMV infections in the same lesion has been described [10].

Neutropenia and agranulocytosis. As neutrophils are innate immune system cells critical for protection against various microorganisms, especially extracellular bacteria and some fungi, neutropenia and agranulocytosis result in a significant risk for infections [3]. The term neutropenia is used to describe a reduction in the number of circulating neutrophils below 1,500 cells/ μ l, while the term agranulocytosis is applied when neutrophil counts drop below 500 cells/ μ l. The characteristic early signs often include fever coupled with oral and/or perianal ulcers [3]. A reduction in peripheral blood neutrophils can occur either because of accelerated removal from the circulation, or due to lack of production in the bone marrow [3]. Lack of production may be limited to neutrophils or include other blood cell populations.

In the oral cavity, crater-like ulcers colonized by large amounts of bacteria and devoid of neutrophils are characteristic of agranulocytosis. Given the patient's age and recent onset of the lesion, the congenital forms of these conditions were not under consideration. Acquired forms can develop secondary to disorders that destroy mature neutrophils in the periphery, or their precursors in the bone marrow.

Diagnosis, Management and Follow-up

Biopsy of the ulcer was performed and revealed variably dense fibrovascular connective tissue partly surfaced by parakeratinized stratified squamous epithelium (Fig. 1b). Most of the surface epithelium was replaced with thick fibrin that contained massive bacterial colonies. Subjacent to the fibrin were dense infiltrates of mononuclear inflammatory cells: lymphocytes, monocytes, macrophages, but no neutrophils. The mononuclear inflammatory infiltrates

spread throughout the granulation tissue of the ulcer bed and deep into the skeletal muscle, where scattered eosinophils were present as well. The histopathologic diagnosis was "traumatic ulcerative granuloma", with a comment that lack of neutrophils in the ulcer suggested a possibility of agranulocytosis. The patient received a prescription for clindamycin and was referred to his physician for CBC and further management.

A week later, the patient was admitted to the NYU Langone Medical Center with complaints of intermittent fevers, pain in the tongue and pain in the anal area. He had a fever of 101°C, a persistent large ulcer on the tongue (Fig. 2), and a fissure in the anal area. The rest of the skin was normal and the chest radiographs showed no abnormalities. There was no significant lymphadenopathy, and neither hepatomegaly nor splenomegaly. Blood and urine cultures were negative for organisms, and the HIV test was negative. CBC showed WBC 1,800/ μ l (normal range 4,200–9,100) with 3% neutrophils (normal range 40–70%), 80% lymphocytes and 15% monocytes (relative increase). Hb = 12.6 g/dl (normal range 13.7–17.5) and platelets = 149,000/ μ l (normal range 150,000–450,000) were

Fig. 2 Clinical presentation of the tongue a day after hospitalization. Note the loss of fibrin, the large size and the crater-like appearance

slightly below normal, while all other blood test values were normal.

The patient's bone marrow was remarkable for complete absence of neutrophils, while megakaryocytes and maturation of RBCs were normal. The bone marrow contained a small number of atypical large CD4⁺ cells.

Collectively, the clinical findings of fever, tongue ulcer, and anal fissure, along with the abnormal CBC and bone marrow findings, were diagnostic of agranulocytosis. The cause of the agranulocytosis, however, was not clear. The patient's hematologist considered that the atypical large CD4⁺ cells were suggestive of lymphoma that could interfere with neutrophil precursors. However, the cells of interest were not monoclonal, and the diagnosis of lymphoma could not be established.

The patient was treated with antimicrobials (vancomycin, cefepime, metronidazole and famciclovir), the immunosuppressant cyclosporine (to target T cells suspected of causing destruction of granulocyte precursors), and granulocyte-colony stimulating factor (G-CSF) to stimulate neutrophil production), which resulted in rapid improvement: within a few days, WBC increased to 5,000/ μ l, and neutrophils increased to 1,000/ μ l. The oral and anal lesions improved, and the patient was discharged 1 week after admission. Treatment with cyclosporine, pegfilgrastim (G-CSF), famciclovir, and trimethoprim-sulfamethoxazole continued on an outpatient basis. Subsequent work-up for lymphoma at another institution was negative. Gastrointestinal problems persisted, but the cause remained undiagnosed.

The patient was subsequently seen at a follow-up visit approximately 1.5 years after hospitalization. According to the patient, the tongue had healed completely soon after his discharge (Fig. 3) and no new ulcers had developed since the first episode.

Discussion

The clinical manifestations of neutropenia/agranulocytosis correlate with the severity in reduction of the neutrophil counts. Chronic neutropenia is commonly associated with aggressive periodontal attachment loss, while agranulocytosis is fatal if not recognized early and treated aggressively, because the risk of septicemia is high [1]. Key features are bacterial infections of mucosal and skin surfaces, particularly the oral cavity, pharynx, middle ear, genitourinary tract, lung, and gut (especially peri-rectal area) that often lack the usual local signs of infection, such as suppuration [11]. Crater-like ulcers may involve the gingivae and/or other oral mucosal sites [1]. In some cases, the ulcers are "punched out", without surrounding erythema, and gingival involvement can lead to widespread

Fig. 3 Clinical image of the tongue at the follow-up visit approximately 1.5 years after hospitalization. There is some elongation of the filiform papillae. Note the scar on the left lateral border of the tongue

necrosis (necrotizing stomatitis) [12]. These infections are usually accompanied by fever and other constitutional symptoms. Particularly helpful signs include fever and rapid development of deep, often crater-like or "punched-out" mucosal ulcers extensively colonized by bacteria and devoid of neutrophils [1]. In the case described here, the thick adherent cover seen at the initial visit produced a smooth elevation that was perceived by the patient as a blister, which could be misinterpreted as a herpetic lesion. The crater-like appearance of the ulcer was evident at a later date, when the fibrin cover came off (Fig. 2).

Causes and Clinical Manifestations of Neutropenia and Agranulocytosis

At the level of the bone marrow, non-selective inhibition of hematopoiesis may lead to a reduction in all blood cells (pancytopenia), which can be caused by diseases that destroy, replace or otherwise shut-down bone marrow, by toxic environmental agents, by infections, or by various cytotoxic medications [3]. Cytotoxic chemotherapeutic agents used for treatment of patients with cancer are especially well-known to produce such deficiencies [3]. Pancytopenia is a feature of aplastic anemia, myelodysplastic syndromes, leukemias, multiple myeloma, and less significantly, megaloblastic anemias [3]. Widespread metastases of solid cancers to bone can also lead to pancytopenia [3]. On the other hand, premature removal of blood cells from the blood can occur in hypersplenism, a complex disorder that results in splenic sequestration of

one or more blood cell types [3]. Several autoimmune conditions are also known to cause blood cell destruction, although these conditions mainly target individual cell populations and are less likely to result in pancytopenia.

Selective inhibition of granulopoiesis can occur by many different mechanisms. Some are congenital disorders, such as severe congenital neutropenia, cyclic neutropenia, and other rare conditions (reviewed by [13]). Neutropenia can frequently be a hallmark of large granular lymphocytic leukemia [14], possibly due to the production of factors that suppress granulopoiesis. Autoimmune destruction of neutrophils occurs in a variety of infections, malignancies and major autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome and multiple sclerosis [15, 16]. However, medications are the most common culprits. In a systematic review of non-chemotherapeutic medications capable of inducing agranulocytosis, 36 drugs were identified as the definite cause, an additional 89 were listed as “probable”, and 11 medications were associated with more than half of published reports [17].

Many antibiotics, including clindamycin, have been implicated in neutropenia and agranulocytosis, the mechanisms of which are poorly understood. Clindamycin in combination with another antimicrobial used to treat 7–14 year-old children with malaria caused a 16% rate of neutropenia [18]. The favored mechanism of non-cytotoxic drug-induced neutropenia is immune-mediated [15, 16, 19], which may be caused by the drug working as a hapten: it binds to cell-surface proteins, modifying their antigenic properties and thus inducing an immune response that by default attacks the drug-bearing cell [3]. A single dose of clindamycin was used to premedicate a 68 year-old male with stable chronic myelogenous leukemia prior to a dental extraction, which 6 days later resulted in neutropenia lasting less than 2 weeks [20]. Previous reports showed that the time required to develop agranulocytosis with antibiotics was less than 19 days [21]. Agranulocytosis occurred concomitantly with drug treatment and resolved when antibiotics were discontinued [21]. Retrospective rechallenge studies suggest that agranulocytosis may be dose related. In all cases, neutrophils were almost completely depleted and the marrow was devoid of granulocyte precursors [21]. In the same study, clindamycin directly suppressed the production of new granulocyte colonies (CFU-G) in one sensitive patient, while 16 normal control subjects showed no such effect.

In the case of the 28-year-old male described in this report, the cause of agranulocytosis remains unknown. However, clindamycin is a potential suspect, in view of the onset of fever and ulcer development within 1–2 weeks of patient treatment with clindamycin for a sinus infection. He received other medications, initially upon developing

this illness, and then started taking clindamycin again, a week prior to admission to the hospital with both oral and peri-anal ulcers. Whether antibiotics are responsible in the current case or not, the ability of antibiotics to induce neutropenia and agranulocytosis poses a dilemma for the management of patients with severe infections that have low granulocyte counts, as they may not only cause further reductions in WBC, but also predispose these patients to other infections not covered by the antibiotic being used.

References

1. Neville B, Damm DD, Allen CM, Bouquot J. Hematologic disorders. In: Oral and maxillofacial pathology, chap. 13. 3rd ed. Philadelphia, PA: Saunders/Elsevier; 2009. p. 581–2.
2. Kumar SKS, Dhyllon A, Sedghizadeh PP. Indurated tongue lesion. Diagnostic challenge. JADA. 2008;139:159–61.
3. Robbins SL, Kumar V, Abbas AK, Cotran RS, Fausto N, Aster J. In: Robbins & Cotran. Diseases of white blood cells, lymph nodes, spleen and thymus. In: Pathologic basis of disease, chap. 13. 8th ed. Philadelphia, PA: Saunders/Elsevier; 2010. p. 588–639.
4. Garg RK, Singhal P. Primary tuberculosis of the tongue: a case report. J Contemp Dent Pract. 2007;(8)4:074–080.
5. Compilato D, Amato S, Campisi G. Resurgence of syphilis: a diagnosis based on unusual oral mucosal lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108:e45–9.
6. Ye'benes M, Toll A, Gime'nez-Arnau A, Ferran M, Parera E, Fraga J, Barranco C, Pujol RM. Pseudotumoral primary syphilis on the tongue in an HIV positive patient. Clin Exp Dermatol. 2008;33:500–22.
7. Inchingolo F, Tatullo M, Abenavoli FM, Marrelli M, Inchingolo AD, Inchingolo AM, Dipalma G. Non-Hodgkin lymphoma affecting the tongue: unusual intra-oral location. Head & Neck Oncol. 2011;3:1. <http://www.headandneckoncology.org/content/3/1/1>.
8. Terada T. Primary non-Hodgkin B-cell lymphoma of the tongue. Br J Oral Maxillofac Surg. 2011;49(5):e18–9. Epub 2010; Oct 14.
9. Kemp S, Gallagher G, Kabani S, Noonan V, O'Hara C. Oral non-Hodgkin's lymphoma: review of the literature and World Health Organization classification with reference to 40 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:194–201.
10. Regezi JA, Eversole LR, Barker BF, DDS, Rick GM, Silverman S Jr. Herpes simplex and cytomegalovirus coinfecting oral ulcers in HIV-positive patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;81:55–62.
11. Bagby GC Jr. Leukopenia and Leukocytosis. In: Goldman: Cecil medicine, chap. 173. 23rd ed. London: Saunders; 2007.
12. Tewari S, Tewari S, Sharma RK, Abrol P. Necrotizing stomatitis: a possible periodontal manifestation of deferiprone-induced agranulocytosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108:e13–9.
13. Rezaei N, Moazzami K, Aghamohammadi A, Klein C. Neutropenia and primary immunodeficiency diseases. Int Rev Immunol. 2009;28:335–66.
14. Mohan SR, Maciejewski JP. Diagnosis and therapy of neutropenia in large granular lymphocyte leukemia. Curr Op Hematol. 2009;16:27–34.
15. Capsoni F, Sarzi-Puttini P, Zanella A. Primary and secondary autoimmune neutropenia. Review. Arthritis Res & Ther. 2005;7:208–14.

16. Schwartzberg LS. Neutropenia: etiology and pathogenesis. *Clinical Cornerstone*. 2006;8[Suppl S]:S5–S11.
17. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med*. 2007;146:657–65.
18. Borrmann S, Lundgren I, Oyakhirome S, Impouma B, Matsiegui PB, Adegnika AA, Issifou S, Kun JF, Hutchinson D, Wiesner J, Jomaa H, Kremsner PG. Fosmidomycin plus clindamycin for treatment of pediatric patients aged 1 to 14 years with *Plasmodium falciparum* malaria. *Antimicrob Agents Chemother*. 2006;50(8):2713–8.
19. Garbe E. Non-chemotherapy drug-induced Agranulocytosis. Review. *Expert Opin Drug Saf*. 2007;6(3):323–35.
20. Bubalo JS, Blasdel CS, Bearden DT. Neutropenia after single-dose clindamycin for dental prophylaxis. *Pharmacotherapy*. 2003;23(1):101–3.
21. Pisciotto AV. Agranulocytosis during antibiotic therapy: drug sensitivity or sepsis? *Am J Hematol*. 1993;42(1):132–7.