Should we consider IgG hypogammaglobulinemia a risk factor for severe complications of Ludwig angina?

A case report and review of the literature

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Abstract

Rationale: Cervical necrotizing fasciitis (CNF) and descending necrotizing mediastinitis (DNM) are rare forms of complication of Ludwig angina. These potentially lethal infections are difficult to recognize in early stages and are often associated with predisposing factors like diabetes and immunocompromised states. Moreover, IgG hypogammaglobulinemia (hypo-IgG) is considered to be a risk factor of mortality in patients with septic shock; however, it is not routinely quantified in patients with extremely serious infections, particularly in cases with no history or evidence of immunocompromising disorders.

Patient concerns: We present a case of a 58-year-old woman who survived Ludwig angina, complicated by CNF and DNM. Despite a rapid diagnosis, aggressive surgical debridement and broad-spectrum antibiotics, the infection and necrosis advanced, requiring multiple surgical interventions and long intensive care unit (ICU) support.

Conclusion: We hypothesize that detecting a low level of endogenous IgG and treating with adjuvant passive immunotherapy was key in determining a favorable outcome.

Abbreviations: AIDS = acquired immune deficiency syndrome, ARDS = acute respiratory distress syndrome, CMV = cytomegalovirus, CNF = cervical necrotizing fasciitis, CRP = C-reactive protein, CT = computed tomography, DNM = descending necrotizing mediastinitis, ER = emergency room, hypo-IgG = IgG hypogammaglobulinemia, ICU = intensive care unit, IVIG = intravenous immunoglobulins.

Keywords: cervical necrotizing fasciitis, descending necrotizing mediastinitis, immunoglobulin, Ludwig angina

1. Introduction

Ludwig angina is a potentially life-threatening cellulitis, in which odontogenic infection from a lower molar perforates the lingual cortex of the mandible, affecting the submandibular, sublingual, and submental spaces bilaterally.[1] Edema of these areas displaces the tongue superiorly and posteriorly producing airway obstruction.[2] Patients may present with neck swelling, pain,

fever, and dysphagia. Nevertheless, the classic manifestations may be absent or masked due to an inappropriate use of antibiotics, steroids, and nonsteroidal antiinflammatory drugs.[3] The mainstay of treatment includes broad spectrum antibiotics, the maintenance of a safe and secure airway and prompt surgical intervention.[4]

The major complications of Ludwig angina are airway obstruction, cervical necrotizing fasciitis (CNF), and descending necrotizing mediastinitis (DNM).[5] CNF and DNM are rarely seen in patients with Ludwig angina and can be associated with an immunocompromised state.[6,7]

CNF is a destructive polymicrobial infection of the fascial planes of the neck, with a reported mortality rate of 7% to 20%. When the disease progresses into the thorax, the mortality rate increases up to 41%.[8] The gas-forming organism (anerobics, *Streptococcus* and *Staphylococcus*)[4,9] associated with this disease can separate fascial planes and extend into surrounding vessels, nerves, muscle and spread to the thorax and mediastinum via the anatomical pathway that connects the base of the skull to the diaphragm.[10] Diagnosing CNF is based on clinical presentation and computed tomography (CT) findings, such as fat stranding and gas tracking along fascial planes. The final diagnosis, however, is confirmed by surgical exploration.[11]

Predisposing factors found to be associated with development of CNF and DNM include diabetes mellitus, extreme age, alcoholism, obesity, tobacco smoking and a compromised immune system, such as the acquired immune deficiency

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syndrome (AIDS) and organ transplantation.[5,9] Additionally, in critically ill adults with septic shock, IgG hypogammaglobulinemia (hypo-IgG) is considered to be a risk factor of mortality and is the most common hypogammaglobulinemia with a prevalence as high as 70%.[12,13] However, it is not an extended practice to monitor the immunological status of patients with severe infections, like Ludwig angina or CNF; especially cases with potentially fatal complications, without known important comorbidities or debilitating medical conditions.

The following is the case of an adult without the typical risk factors for Ludwig angina but with hypo-IgG that survived catastrophic complications of this infection.

2. Case report

A 58-year-old, previously healthy female, saw her dentist for multiple tooth implants. The procedure was completed without complications, and, because of a history of penicillin allergy, the patient was discharged with erythromycin as antimicrobial prophylaxis. A few days later, she presented to the emergency department with a history of progressive facial and neck swelling. She was afebrile, blood pressure of 118/76 mm Hg, heart rate of 81 ppm, and an oxygen saturation of 95% in room air. Initial physical examination revealed neck edema, erythema, and bilateral submandibular and submental tenderness. Laboratory data revealed: white blood cells (8600 cells/mm^3), neutrophils (7790 cells/mm^3), and increased serum C-reactive protein (CRP): 398 mg/L. A cervical CT scan showed abscess in the floor of the mouth with horseshoe morphology suggestive of Ludwig angina, with multiple gas inclusions in the submental space. The abscess extended to the retropharyngeal space and descended into the mediastinum. An extensive mediastinal fat trabeculation and air bubbles suggestive of mediastinitis was observed, with areas of necrosis and fluid accumulation surrounding the aorta, posterior mediastinum, and the esophagus. Additionally, a right empyema was present (Fig. 1A and B). Empirical intravenous antibiotic therapy was started with meropenem (1 g every 8 hours) and clindamycin (600 mg every 8 hours).

The patient was taken to the operating room (OR) for surgical debridement and tracheostomy. Lateral thoracotomy was performed and a large anterior mediastinal abscess surrounding the trachea and superior vena cava and an extremely fetid empyema drained approximately 700 mL of pus. Furthermore,

Figure 2. Extensive debridement of anterior neck, bilateral submandibular, and sublingual spaces.

necrosis of the mediastinal pleura was observed. The mediastinal and pleural spaces were intensively irrigated with 3% hydrogen peroxide, and debridement of all necrotic areas was performed. A digital blunt dissection around the superior vena cava, trachea, and aortic arch was achieved in order to drain all the affected compartments. Intraoral and bilateral transcervical incisions were completed, and extensive debridement of the anterior neck, bilateral submandibular, and sublingual spaces were carried out. Additionally, widespread areas of fascial planes and musculature were necrotic. Penrose drains were inserted through the open
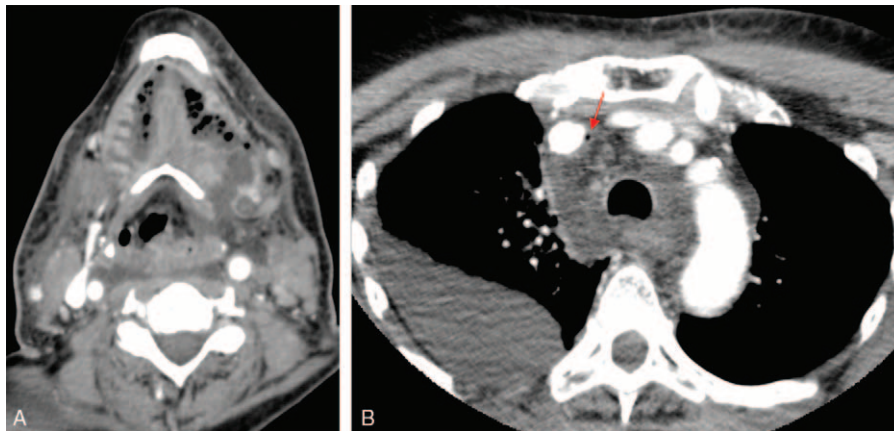
Figure 1. (A) Abscess in the floor of the mouth with horseshoe morphology with multiple gas inclusions in the submental space. (B) In superior mediastinum, fat trabeculation, fluid collection, and air bubbles suggestive of necrotizing mediastinitis. Right pleural effusion compatible with empyema. Red arrow: small air bubble adjacent to innominate truncus.

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wound to communicate the anterior and lateral cervical planes with the floor of the mouth (Fig. 2). Twenty-four hours later, because of diffuse areas of purulent and necrotic tissue, new surgical debridement was performed. A more extensive skin resection was done. Wound cultures were positive for mixed flora consisting of *Streptococcus constellatus*, *Prevotella buccae*, *Gemella morbillorum*, and *Parvimonas micra*, however, given the patient's critical condition and active ongoing signs of infection, with open cervical wounds, we decided to maintain treatment with meropenem and clindamycin. After 2 weeks of admission, the antibiotic spectrum was narrowed to intravenous piperacillin–tazobactam.

The patient developed a septic shock and multiorgan dysfunction, requiring high doses of intravenous norepinephrine and support with continuous renal replacement therapy for acute renal failure. On the 8th day of admission, she was transferred again to the OR where new cutaneous necrosis and multiple purulent collections were observed, specifically in the parapharyngeal, submandibular and deep prevertebral space, as well as in the parotid compartment. The ear–nose–throat surgeon described a new progression of the necrotizing fasciitis affecting all the cervical spaces and a great amount of purulent tissue had to be drained. Blunt dissection of prevertebral, supraclavicular, and thyroid space was performed (Fig. 3). New samples were sent to culture, revealing growth of *Candida glabrata*. With these results, we added anidulafungin to the treatment for a total of 21 days.

After more than 7 days in an extremely critical condition, her hemodynamic parameters slowly started to stabilize. Open wound therapy, with daily aggressive debridement and irrigation with saline solution was continually performed in the intensive care unit (ICU). Because of persistence of the loculated effusion despite chest tube drainage, we placed a new eco-guided posterior pig-tail and started fibrinolytic therapy, as well as continuing with pleural irrigation with saline solution.

Several neck and chest CT scans were consecutively done. All the collections of deep neck spaces had been improving. However, in the anterosuperior mediastinum an alarming collection of 41 mm × 14 mm in close contact with the aortic arch persisted. Thoracic surgery specialists advised conservative management of this collection. On day +26, we detected a new abscess in the left axillary region and in the supraclavicular fossa.

Figure 3. Intraoperative image after a new extensive debridement.

For the fourth time, the patient was taken to the OR where drainage through blunt dissection was done.

The patient had a torpid evolution following the last surgical intervention, with multiple complications and an extended ICU stay. She developed severe acute respiratory distress syndrome (ARDS), with reactivation of cytomegalovirus (CMV) infection (800 copies on the bronchoalveolar lavage), *Enterobacter cloacae* bacteriemia and urinary tract infection by *Klebsiella pneumoniae* resistant to carbapenems (OXA-48). With these results, we rotated antibiotics to meropenem and amikacin, and added ganciclovir to the treatment (5 mg/kg every 12 hours for a total of 21 days).

On day +40 of ICU admission, we did a complete screening of the patient's immunological situation: quantification of immunoglobulins, complement proteins, T cells (CD4, CD8, CD4/CD8), immunophenotypic TCD3$^+$, TCD4$^+$, TCD8$^+$, B lymphocyte CD19$^+$ and NK cell. All the results were normal except for a hypo-IgG of 548 mg/dL; IgG1: 300 mg/dL; IgG2: 164 mg/dL, and IgG4: 5.3 mg/dL (normal reference values in our laboratory: IgG: 700–1600 mg/dL, IgG1: 402–715 mg/dL, IgG2: 216–523 mg dL, and IgG4: 9.0–104 mg dL). Based on these results and the persistence of her deteriorated clinical condition, we decided to treat with intravenous immunoglobulins (IVIG) (Flebogamma, Instituto Grifols, S.A. Barcelona, Spain) at a fixed dose 25 g (400 mg/kg weight) every 15 days, for a total of 3 doses. Follow-up IgG quantification was done 3 and 8 weeks after the last IVIG dose, the values were 688 and 673 mg/dL, respectively.

The patient remained in the ICU for a total of 82 days. Her hemodynamic and inflammatory markers gradually improved, as well as her respiratory status. She was successfully weaned off mechanical ventilation. A rapidly formation of granulation tissue and reepithelialization was observed, without the need of a reconstructive surgery. Because of severe dysphagia and refractory sialorrhea, she was discharged to a regular ward receiving enteral nutrition through a percutaneous radiologic gastrostomy. After a long period of physiotherapy and oral neuromuscular reeducation, she was able to eat again, the tracheostomy was eventually decannulated and the patient was discharged from the hospital 137 days after admission (Fig. 4).

3. Discussion

This dramatic case clearly demonstrates that modern times can still surprise us with serious old-fashioned problems. In the literature, there is a lack of studies able to describe so many important and severe complications of Ludwig angina following a dental surgery, illustrated in only 1 patient: CNF, DNM, pericarditis with arrhythmic storm, pericardial and pleural effusions, septic shock and ARDS with reactivation of CMV and multiorgan failure. Based on our patient's symptoms and history of prior dental procedure, a deep neck infection was rapidly suspected in the emergency room (ER) and a CT scan of her neck and thorax was performed. Despite a high suspicion, by the time the diagnosis was confirmed, we were already far behind in this rapidly spreading infection.

A contrast CT scan represents the cornerstone, not only to assist in the diagnosis of CNF and DNM, but also to show the extent of disease, evaluate any serious complications, and guide decisions regarding surgical approaches when indicated.[14,15] In addition, ultrasound is a reliable supplement modality to CT scan, specially at the patient's bedside, for example, to place a drainage and to differentiate edemas from abscess collections.[16] In our patient, a close follow-up CT was essential in order to

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Figure 4. Six months after hospital discharge.

determine the adequacy of drainage, monitor the evolution of the process, and identify recurrent abscesses and progression of DNM.

Management of CNF includes early surgical incisions and debridement of necrotic tissue, broad spectrum intravenous antibiotics, and airway control. In a recent analysis of 59 cases with CNF, Elander et al[17] found that early surgical debridement combined with hyperbaric oxygen treatment may be associated with an increase in survival rate. In case of secondary DNM, the surgical approach should combine aggressive cervical and mediastinal drainage of all involved spaces as well as adjacent potential areas.[18]

Severe deep neck infections and DNM are often associated with baseline immunological diseases and other debilitating comorbidites, like diabetes and alcoholism.[5,9,19] However, to the best of our knowledge, cases of CNF and DNM in patients with hypo-IgG have not been previously reported. Low levels of immunoglobulins are a frequent finding in patients with septic shock. In the studies that excluded immunodeficiency states, hypo-IgG has been associated with an increase in the risk of severe illness, a greater incidence of ARDS and longer duration of shock.[20,21] Bermejo-Martin et al[22] found that IgG1 was the only immunoglobulin independently associated with mortality.

We were unfamiliar of the immune status of our patient on the first days of admission, and we cannot confirm if detecting and treating a low IgG earlier would have given our patient a less severe illness, or a faster resolution of the process. We definitely missed the so called "window of opportunity" for IVIG (first days that follow clinical presentation of sepsis). Furthermore, there is still a lack of consensus on the optimal dosage and timing of administration. The dose used in randomized, placebo-controlled clinical trials and observational studies varies from 0.2 to 2 g/kg.[23–26] Our dose was within this range, and given every 15 days based on immunoglobulins levels and the clinical status of the patient.

During follow up we found that the patient had a partial deficit of IgG. Even though an improvement of IgG levels were observed and concurred with the favorable evolution of our patient, 2 months after hospital discharge, she continues to visit the immunologist specialist and her IgG values persist under the normal reference value (644 mg/dL).

In conclusion, fulminant infections complicating odontogenic processes can have diverse presentations. Patient's clinical status may rapidly deteriorate; therefore early diagnosis and treatment are necessary to reduce mortality. The maintenance of a secure airway is paramount, being air-way obstruction and spread of infection to the mediastinum the most feared complications. Patients presenting with a life threatening infection and that additionally lack coexisting comorbidities or a previously known immunodeficiency, such as the one we describe, should consistently be evaluated regarding their immunological situation. This includes measuring endogenous levels of immunglobulins, complement proteins, T cells, or the evaluation of percentages of circulating CD4+ CD25+ T-regulatory cells in blood.

Acknowledgments

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