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Maxillary Reconstruction Timing in Severe Systemic Lupus Erythematous (SLE) Patient with Bone Destruction due to Invasive Aspergillosis: Case Report

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Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease that targeted to multi organs with various manifestations. This disease affected mostly young women. The most cause of mortality in SLE patients is infection.[1] Aspergillus infection is commonly found in the SLE population. Primary immunity dysfunction in SLE and regimen therapy, such as pulse dose corticosteroids, long term corticosteroids, immunosuppressant, and biological agents increase the risk of infection in SLE. Based on a study in New York, among 233 SLE patients, there were 150 cases of infection, of which 23 were opportunistic infection: 12 were candidiasis while 11 others were deep fungal infection.[2] In a retrospective study from Taipei with a total of 6714 subjects, 393 cases met the criteria for inclusion. Cryptococcus spp., Aspergillus spp., and Candida spp. were the most common fungal pathogens. Cohorts described Invasive Fungal Disease (IFD) in 0.6-3.2% of SLE inpatients and 0.28% of SLE outpatients. IFD occurred at a median of 2 years of disease duration (IQR: 0.5-7.1), and 39% of cases occurred within the first year of SLE. Disease activity and corticosteroid dose >60mg/day emerged as risk factors for IFD. IFD was associated with a mortality rate of 53% (161/316 cases), and worse in the absence of antifungal therapy (n = 43).[3]

The recommendation of Severe SLE management by American College Rheumatology (ACR), European League Against Rheumatism (EULAR), and Indonesian Rheumatology Association (IRA) suggest to give pulse dose steroid 500 mg - 1 gr for 3 days, and if it does not give an adequate response, continued with cyclophosphamide (CYC) injection 500-750 mg/m^2 per month then every 3 months thereafter depending on clinical response. The usual duration therapy is 2-2.5 years.[1,4,5] Therapy of pulse dose corticosteroids, long-term corticosteroids, and immunosuppressants can significantly increase the risk of aspergillus infection. A study by Hung et.al, reported that high daily steroid dosing, recent pulse steroid therapy, azathioprine, rituximab, concurrent infections, and CMV viremia were mortality risk factors for invasive Aspergillosis (IA) in SLE.[3]

In this case, a Severe SLE patient was in the third of 28-days-cycle cyclophosphamide chemotherapy when the early symptoms

of aspergillus infection occurred. This then developed into extensive cranial bone damage. Later it was planned to get a biopsy and debridement for bone and soft tissue to diagnose and therapy palate osteonecrosis, followed by reconstruction surgery. This case report aimed to report the successful management of a severe patient on chemotherapy undergoing several operations so that the SLE aspergillosis is optimally managed.

Case

A 21 years old single woman who has been diagnosed with SLE since 2009 had arthritis, mucocutan, serositis, vasculitis, nephritis, Anti-Nuclear Antibody (ANA) positive, and dsDNA positive as the early manifestations. From 2009 until 2018, the SLE activity fluctuated but still could be controlled with oral medications. Since September 2018, she has been receiving 28-days-cycle CYC chemotherapy to treat the nephritis manifestation. In the third chemotherapy on December 21st, 2018, she felt a lesion on her hard palate, then followed with swelling gums with red edges, and unsteady teeth. Some weeks later, her teeth started falling out without any pain. The lession on her palate widened until torn her palatal mucosa. She sometimes felt mild fever, congested nose, rhinorrhea with a serous secret and unpleasant smell. However, she did not feel any arthritis, mouth ulcer, hair loss, photosensitivity, fever, cough, breathlessness, vomit, difficulty in defecation, and urination. The routine therapy at that time was Mycofenolat Acid (MPA) 2 x 360 mg, Methylprednisolone 4 mg 1-1-0, Cetirizine 1 x 10 mg, Irbesartan 1 x 300 mg other than CYC chemotherapy every 28 days.

The physical examination, obtained moderate pain, fully alert, underweight with BMI 14.2 kg/m^2 and BSA 1.2 m^2. The blood pressure was 112/75 mmHg, the pulse rate was 78x/min, the respiratory rate was 20x/min, and the temperature was 36.7^o Celsius. There was diffuse alopecia, hyper pigmented malar rash on her face, and unpainful red swelling under her right eye. Dry and cracked lips were found. In the mouth cavity, her hard palate tore until half of the surface demonstrating a yellowish-white tissue was visualized, mouth mucosal tissue was pale with red edges and irregular but it was not soft and fragile, with no bleeding or pus. Some of the superior molar teeth had fallen. Her thorax, heart, lung, and abdomen were normal. There was minimal

Figure 1. Patient's condition before and after suffered Invasive Aspergillosis.

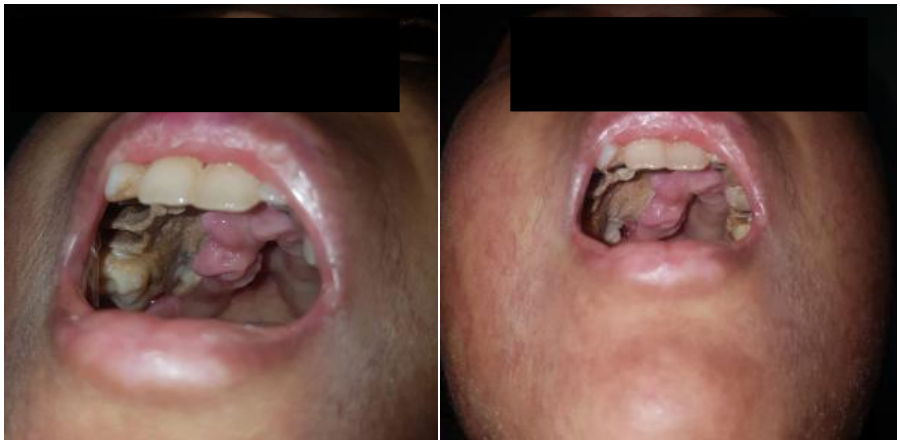

Figure 2. Lesion in hard palate.

pitting edema on her feet. The patient's MEX SLEDAI score was moderate activity (renal dysfunction, mucocutan, and mucosal ulcer).

Complete blood examination oin December 19th, 2018 showed Hb 10.6 d/dl, Leucocyte 11.92.10^3 /mm^3, Platelet 417.10^3 /mm^3, Segment 82, Lim 14.3, Mon 3.6, Eos 0, Bas 0.1, Neutrophil Count 9780/mm^3, Lymphocyte Count 1700/mm^3, IGRA negative, BUN 8mg/dl, Creatinin 0.54 mg/dl, Blood glucose 120 mg/dl, SGOT 18 md/dl, SGPT 5mg/dl ,Albumin 2.75 mg/dl, Sodium 134 meq/l, Potassium 3.81 meq/l, Chloride 99 meq/l.

Routine urine examination revealed clear yellow, normal smell, pH 7, density 1.015, Bil.-, Uro. Normal, Ket.-, Nit.-, Leukocyte Esterase -, RBC 22, Blood neg, Leu 14, Glucose neg, Prot +2, Bacteria 18.4, Yeast 0, Small round cell 25.3, Sil pathologist (-). Chest Radiology and Electrocardiography result were normal.

The patient was consulted to Mouth Surgery Outpatient Clinic, then plain and non-contrast Head MSCT was performed, and showing Bilateral frontotemporal Lobe Atrophy, Cavum Vergae Dilatation, Pansinusitis, Osteodistruction of Bilateral maxillary Bones, Bilateral Zygomatic Bones, Right Frontal Bone, Bilateral Temporal Bones, Sphenoidal Bone, and Right Mastoiditis.

Nasoendoscpy was performed by otorhinolaryngology showing Atrophic turbinate, Oronasal fistula, and discharge from medial meatal. The differential diagnoses after discussing with mouth surgery and ENT department were: Chronic RhinoSinusitis, Soft palate ulcer, maxillary/zygomatic/frontal/ethmoid osteonecrosis due to SLE DD osteonecrosis induced corticosteroids DD lethal midline granuloma. The therapy was Nasogastric Tube for feeding, Amoxicillin-clavulanate 3x625mg, NAC 3x1, continuing CYC chemotherapy, stopped methylprednisolone, planned for bone and soft palate biopsy if it was possible.

At that time, a biopsy could not be performed due to unstable SLE activity and she was still in CYC chemotherapy every 28 days. If she underwent surgery at that time, the risk of bleeding and prolonged wound healing would increase. Thus, the biopsy was planned in the 3 months cycle of chemotherapy. While waiting for the 3-months-cycle chemotherapy, her lessons grew progressively without any sign of healing.

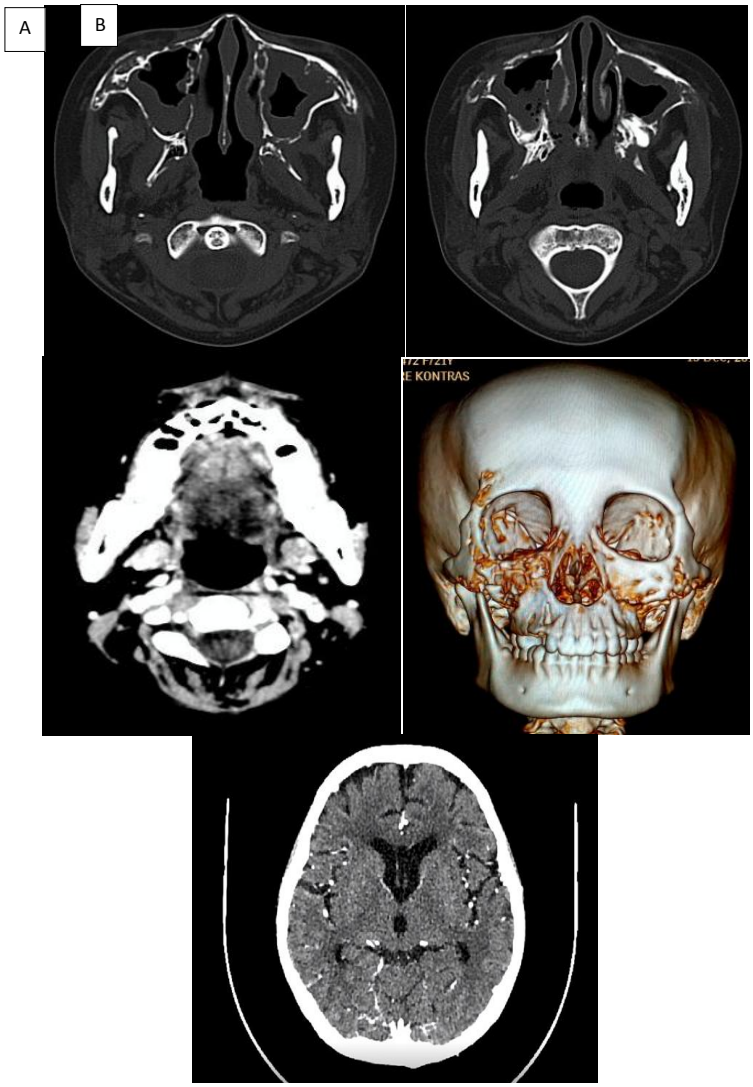

Figure 3. Head MSCT non-contrast (A) and contrast (B) Finding.

On May 7th, 2019, or about 4 weeks after the first chemotherapy of the 3-months-cycle chemotherapy, a biopsy of bone and soft tissue was performed in the hard palate and nasal area. During surgery, the bleeding was minimal and the wound healing was quick, so that 5 days after her surgery, she could go home. The histopathology results from the soft tissue biopsy were Maxillary tissues: Invasive Aspergillosis, Soft tissue between Maxilla and nasal cavity: The tissues covered by ciliated pseudostratified epithelia, it is likely from the aspergillosis infection. Bone biopsy: Alveolar biopsy: necrotic bone, Biopsy from the mucosal border: chronic inflammation of connective tissues, likely due to aspergillosis. At the time we did, the secret culture was not performed.

The therapy after knowing the histopathology result was continuing CYC chemotherapy 3 months cycle, Fluconazole 50 mg per day, Irbesartan 1x300mg, and if there was no longer infection, the palate reconstructive surgery could be performed. After antifungal therapy for 6 months, the

Figure 4. Patient after therapy and reconstructive surgery.

lesion improved, there were no new lession and granulation tissue began to grow. Repeated biopsy showed Aspergillus infection was overcome. However, she still had a mouth cavity and nasal deformities, causing her difficulty to speak and swallow.

From October to December 2019, a reconstructive surgery by mouth surgeon, ENT, plastic surgeon, and the periodontal specialist was performed. The outcome of that surgery was satisfying. She got an obturator after removal of her damaged hard palate, and then placed the dentures. Finally, she could speak and eat well.

Discussion

As it is recommended in SLE management, CYC is the therapy for severe SLE cases, such as nephritis, a neuropsychiatric disorder, severe thrombocytopenia autoimmune hemolytic anemia, severe pneumonitis, alveolar hemorrhage, abdominal vasculitis, and extensive skin disorder. This therapy is administered together with high or pulse-dose glucocorticoid which is continued with long-term oral dose glucocorticoid.

Cyclophosphamide is one of the alkylating agents used for cancer and immunosuppression therapies. Cyclophosphamide is a prodrug changed in the liver into an active metabolite in the form of phosphoramide mustard, which then binds with DNA and RNA crosslinks and later inhibits the replication of DNA and protein synthesis. In low dose CYC function as immunosuppression through several mechanisms, selectively depleting of Tregs and inhibition of their suppressive function; switching the secretion of cytokines from Th2 to Th1; and enhancement of Th17, memory, and effector CD8 T-cell phenotypes.[7]

The side effects of CYC may include nausea, vomiting, leukopenia, thrombocytopenia, alopecia, and anorexia. Other symptoms may include skin pigmentation, oral mucosal ulceration, and sterile hemorrhagic cystitis. It can also cause non-specific dermatitis, pigmentation of the nails, regrowth of hair, anemia, hematuria, fibrosis of the ovaries, gonadal suppression resulting in amenorrhea or

azoospermia, hemorrhagic colitis, and jaundice. It may result in damage to the hair follicles, short-term dizziness, transverse ridging of the nails, and hepatic toxicity. Secondary neoplasia and nephrotoxicity have also been reported. Other symptoms may involve skin irritation, gastrointestinal disturbances, and hepatic dysfunction. High doses over a prolonged period can cause interstitial pulmonary fibrosis. Other symptoms of exposure may comprise granulocytopenia (causing susceptibility to infection and opportunistic infection), myocardial damage, interstitial pneumonia, and hypoplasia of all elements of bone marrow. It has been known to cause blurred vision, pulmonary fibrosis, cardiomyopathy, and sterility. Fetal abnormalities can occur if it is ingested during pregnancy. Eye contact can cause transient blurring of vision, dry eye syndrome, viral and another keratitis, and severe keratoconjunctivitis associated with graft-versus-host disease leading to scarring of the corneas. It may also result in lymphocytopenia.[8]

This patient is an SLE patient who was diagnosed 9 years ago. She had an unstable SLE activity. Long-term corticosteroids consumption and immune-suppressants led her to an immune-compromised condition. In the late 3 months before infection, she got pulse dose steroid as lupus nephritis indication, then followed with CYC chemotherapy. These conditions depressed her immunity more. This immune-compromised condition caused her to suffer from severe aspergillus infection formed as sinus invasive aspergillosis of extrapulmonary aspergillosis. There was a relationship between a low level of neutrophil and Invasive Aspergillus Infection. A neutrophil is innate immune protection and the first line against infections such as aspergillus and candida. In neutropenic patients, the lack of host response is associated with rapid growth, which induces necrosis of host tissues and facilitates fungal nutrition.

Our patient's complaints were matched with sinusitis aspergillosis manifestations such as fluctuating fever, headache, nasal congestion, and rhinorrhea, widened lesion in palate until some teeth fell out without any pain. Invasions to the brain, eyes, and skin were not found. Lung, heart and abdominal examination were normal. From Head MSCT both plain and contrasted imaging, there was thickening of mucosal walls in the bilateral maxillary, bilateral ethmoid, sphenoidal, and frontal sinuses. Air cellular mastoid was decreased, destructions in right maxillary bone, right zygomatic bone, right frontal bone, bilateral temporal bones, and sphenoid bone. The findings of the Head MSCT supported bilateral frontotemporal Lobe Atrophy, Cavum Vergae Dilatation, Pansinusitis, Osteodistruction of Bilateral maxillary Bones, Bilateral Zygomatic Bones, Right Frontal Bone, Bilateral Temporal Bones, Sphenoidal Bone, and Right Mastoiditis. However, this result could not show specifically of any invasive aspergillosis. The non-specific CT imaging did not show mass, bony dehiscence, thickening of extraocular muscles, inflammatory changes of the orbital and orbital apex, or mucus secretions. We used MRI is used to evaluate soft tissue widening from sinus to pericentral fat, sinus cavernosus, and brain. Her palate bone and soft tissue histopathology result showed invasive aspergillosis with bone and soft tissue destruction. As in the EORTC/MSG Consensus, the patient was diagnosed with Proven Invasive Fungal Disease.

Several therapeutic strategies have been applied in an attempt to improve the outcome of IA. These include the introduction of potent antifungal agents, surgical excision of sequestered necrotic lesions; and, in selected patients, and the use of immune-modulating

agents such as in neutropenic patients. In our case, a set of operations were done, starting from biopsy until a few maxillary bone reconstructive surgeries due to severe damage.

The problem is out the case was the right timing for performing surgery, our patient was still in unstable SLE condition and on CYC therapy. To date, there has been no guideline or recommendation regarding perioperative management of severe SLE patients undergoing CYC therapy. Several considerations in conducting surgical procedure are:

1. SLE patients suffer from a higher rate of infections, which appears it is related to both an intrinsic susceptibility and treatment-related immunosuppression. Immunological dysfunction may be due to functional asplenia, impaired complement system, and mannose-binding lectin deficiency, a serum protein that binds mannose in the bacterial wall and activates the complement system.[9]
2. Prolonged postoperative wound healing in patients with immunosuppression.[10]
3. The side effect of CYC therapy in the form of cardio-toxicity is a recognized complication of high-dose cyclophosphamide therapy, with acute decompensation. [9]
4. Medullar suppression is the most important toxic effect caused by almost all chemotherapeutic drugs, except bleomycin and vincristine. There are lymphocytopenia, variable thrombocytopenia degrees, erythropenia and hemophilic, anemia. Neutropenia or lymphopenia arising secondary to CYC usage can predispose people to a variety of bacterial, fungal, and opportunistic infections. [10]
5. Cyclophosphamide reduces plasma pseudocholinesterase concentrations which may last for several weeks after infusion, leading to prolonging the effect of succinylcholine, and may result in prolonged neuromuscular blockade when administered concurrently with succinylcholine.[10]

Some studies suggested surgery between 2 and 5 weeks after the last chemotherapy cycle. In practice, surgery is usually performed when the neutropenic window is overcome, normally resulting in a 3- to 4-week interval.[11]

In the Brazilian Technical Bases Manual, it is specified that adjuvant chemotherapy should be initiated, at the most, between 30 and 60 days post-surgery. However, the time to be waited for undertaking the other chemotherapy cycles is not specified. [12]

In our case, the first surgery was performed 4 weeks after the first 3-month cycle of chemotherapy. The SLE activity was stable and the neutrophil count was within the normal limit. The surgery went well despite minimal bleeding which was manageable. The surgical wound was healed quickly without secondary infection. Five days after the surgery, the patient was discharged. Based on histological examination, the patient received an antifungal drug. Significant clinical improvement was achieved after 6 months of antifungal therapy. The tissue damage was no longer extensive granulation tissue started growing in the gum and palate.

The next surgical procedure performed was serial reconstruction which was conducted after the third 3-month cycle of cyclophosphamide chemotherapy, which was 4 weeks after chemotherapy. After the third 3-month-cycle chemotherapy, the activity of SLE was mild and stable so that cyclophosphamide chemotherapy was stopped and continued with oral DMARD consisting of MPA and a low dose of Methyl

Prednisolone. The whole set of reconstruction surgery went well without postoperative complication as well as stable SLE with mild activity.

Conclusion

Systemic Lupus Erythematosus patients have a high risk to suffer from invasive aspergillosis due to immune-compromised conditions caused by SLE immunity dysregulation, consumption of immunosuppressant agents, high dose and long term intake of corticosteroids.

Invasive aspergillosis therapy inpatient undergoing chemotherapy comprises the combination of antifungal drugs, surgery, and chemotherapy dose reduction. In SLE patients receiving CYC, it is required to be cautious when choosing the right time for surgery between chemotherapies to obtain well-controlled SLE with good surgical outcomes.

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