Necrobiotic Xanthogranuloma Sucessfully Treated with Cyclosphospamide-Methyl Prednisolon

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ABSTRACT

Objective: Necrobiotic Xanthogranuloma (NXG) is a rare, chronic, and progressive disease that provokes skin lesions, such as damage of the histiocytes of Non-Langerhans cell, skin lesions (yellowish or noduled ulcerative lesions) in the induration skin. The most common predilection areas are on the face, orbital, and extremities. The etiology is still unknown, but sometimes is often associated with monoclonal gammopathy. The granulomatous infiltrate was composed of lymphocytes, epithelioid cells, foamy histiocytes and giant cells, many of them of Touton type. Some patients who had lesions are asymptomatic, sometimes they will feel paresthesias, burning pain. Nowadays, this management still vary widely, include medicamentous (cytostatics, steroids), radiotherapy, and surgery. Sets forth the results of two patients NXG.

Methods: The subjects in this study were a 44-years-old male patient with some lesions on both cheeks and forehead since 5 months ago and a 29-years-old female patient with some lesions on both cheeks and ears.

Results: First patient treated with *Methylprednisolon* 0.8 mg/Kg and tappered off for a month with improved results. Second patient treated with *Cyclosphosphamide* 750 mg/m^2 with improved results within three weeks.

Conclusion: Necrobiotic Xanthogranuloma treatment still required further research by the number of samples that much to find out the efficiency management NXG.

Keywords: Cyclosphosphamide, methylprednisolon, necrobiotic xanthogranuloma

Introduction

Necrobiotic Xanthogranuloma (NXG) is a rare disease, a chronic, progressive and cause skin lesions in the form of damage to the cell Non-Lagerhans histiocytes. Necrobiotic Xanthogranuloma was first described in 1980 by Winkelmann as Kossad and 8 patients with NXG which have monoclonal gammopathy, especially IgG kappa type 2. More than 100 patients with NXG has been studied, approximately 80% of patients with monoclonal gammopathy associated. Monoclonal gammopathy is a condition characterized by the onset of an abnormal protein, known as a monoclonal protein or M protein in the blood stream. These proteins are produced by plasma cells of a type of white blood cells that mature later became the B lymphocytes, produce antibodies to fight infection in the body. The emergence of this protein in the body usually does not cause damage and gejala.[1-3]

Skin lesions are hard to find, but in a series of cases by Mehregan and Winkelmann, more than 20% with hepatomegaly and splenomegaly. Hematologic abnormalities may include neutropenia, cryoglobulinemia, hypocomplementemia, and hyperlipidemia. Systemic involvement may include multiple myeloma, Hodgkin lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, lymphoma or Waldenstrom limfoplasmatik, lung disorders, or heart. Plasma cell dyscrasias monoclonal gammopathy (MGUS), 80% of patients had either type of IgG kappa or lambda light chain. Chen et al reported the first case in conjunction with the plasma cell dyscrasias and lymphoproliferative disorders, although the involvement very rendah.[1,2]

Necrobiotic Xanthogranuloma can damage but is local, has the potential to affect multiple organ systems, including the eyes, spleen, muscles, lymph nodes, and central nervous system. Silvak-Callcott NXG et al studied 137 cases in adults in the area of orbital and ocular adnexal. Patients with periorbital area may experience changes such as vision, diplopia, proptosis, episcleritis, keratitis, iritis, conjunctivitis, and perforation cornea.[1,2]

Clinical features NXG is infiltration with slow progression and damage as well as skin lesions that describe tissue damage and systemic. Lesions may become indurated ulcer with yellow or discolored. Plaques and lesions involving the limbs and extremities, but more than 80% of patients present with periorbital disorder. Most patients had lesions are asymptomatic, but can also appear with symptoms such as pruritis, paresthesias, and burn sensation.[1,2]

Necrobiotic Xanthogranuloma pathophysiology can not be explained with certainty. One hypothesis says that paraprotein serves as autoantibodies to induce fibroblast proliferation and deposition of dermal macrophages. Another hypothesis says paraprotein lipoprotein

receptor will bind to monocytes then will stimulate the formation of cells xanthomatos stored in the skin so that the granulomatosis. Starting presence of foreign body giant cell reaction, causing an increase in skin deposition, serum immunoglobulins and lipid complexes, then there was a secondary proliferation of macrophages that cause high paraprotein paraprotein and granuloma formation of the lipoprotein, which will bind histiocytes reseptor.[5-7]

Necrobiotic Xanthogranuloma discovered histopathologic contained macrophages and foam cells in the dermis, subcutaneous tissue, extensive necrobiosis, touton giant cells, and lymphoid follicles. The presence of cholesterol in the area necrobiosis klef used to distinguish NXG with other granulomatos inflammation.[6-9]

Necrobiotic Xanthogranuloma is difficult to treat and recurrence after surgery is very high. Although there is no modality that shows the effectiveness of treatment options including glucocorticoids (topical or systemic), alkylating agents, interferon alpha, antimetabolite, antibiotics, thalidomide and plasmaperesis. One patient with extensive involvement of the face was treated with a total of 6 cycles of 0.5 mg / kg / day of intravenous immunoglobulin (IVIG) for 4 days with intervals of 4-6 weeks. After 6 cycles, showing resulosi almost complete and biopsy specimens from the area previously shown complete resolusi.7 Another case shows the resolution for 4-week low-dose prednisone (0.5 mg / kg), in some cases NXG unrelated to paraproteinaemia. Another case shows the isolation NXG with 47 therapy psoralen and ultraviolet A (PUVA) fotokemoterapi.[1,6-9]

Surgical skin is still limited role as a palliative intervention. Surgery can lead to high recurrence of about 42% with post-operative lesions greater than ever. CO2 laser treatment may be performed as an alternative to palliative therapy in patients who have a medical failure.[6-9]

Papagoras and Kitsos of Greece conducted a study of a man aged 53 years with abnormal swelling in both eyelids, cheeks, and there is discoloration of the skin and the resulting pain. Patients given cyclosphospamide for 6 months at a dose of 750 mg / m2 and a combination with methyl prednisolone 0.8 mg / KgBW tappering off. After treatment with these patients experiencing perbaikan.[4]

Case

The first case, man 44 years old chief complaints swelling on both cheeks and forehead. since 5 months with swelling process that happens gradually. Swelling felt no pain and no other skin disorders. Not found family history of suffering from the same illness.

On physical examination, the status of generalists within normal limits. Localist status are swelling of the cheeks and forehead defined, cystic, mobile and non-tender.

In the complete blood laboratory examination; within normal limits. Urinalysis, liver and kidney function, serum lipid profile within the normal range. Chest X-ray within normal limits and

Results of histopathological examination of biopsies on both cheeks showed a rounded oval-shaped cells grouped to form a granuloma structures, the cells seem to resemble epithelioid cells, the cell nucleus chromatin smooth monotonous form. Many multinucleated giant cell found scattered or in groups, many also found foam cells (foam cells) with the conclusion necrobiotic xanthogranuloma.

Our patient management of the methyl prednisolone tappering off each 5 days at a dose of 32 mg, 24 mg, 16 mg, 8 mg, 4 mg. After giving the full complaint methyl prednisolone reduced swelling in the face and disappeared since the 16 mg dose. Currently the patient in preparation for giving cyclosphospamide.

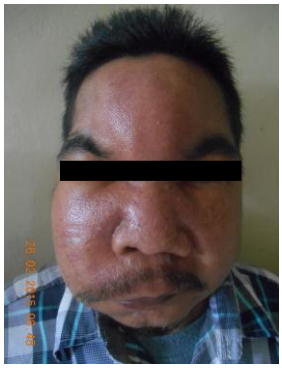

Figure 1. Clinical Picture Before Giving Methyl prednisolone

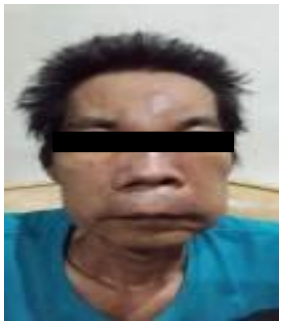

Figure 2. Since 1 month ago raised bumps back on the face

The second case: A 29-year-old woman, an outpatients with major complaints bumps on the face of perceived since 5 months ago. Initially felt itchy on both cheeks and then the longer growing louder and a little felt numbness.

On physical examination in a second region of the left cheek and preaurikuler obtained with soft tissue thickening of skin discoloration on it, looks more black than the normal area.
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On physical examination in a second region of the left cheek and preaurikuler obtained with soft tissue thickening of skin discoloration on it, looks more black than the normal area.

In the laboratory examination complete blood within normal limits. Urinalysis, liver and kidney function, serum lipid profile within the normal range. Chest X-ray within normal limits and

Results of histopathological examination on both cheeks and preaurikuler the left shows a mass of necrotic amorphous, tiny pieces of necrotic tissue, many histiocytes / cell foam (foam cells) are proliferative, partially solidified to give the impression of hyperplastic and also found some multinucleated giant cell, nucleus polymorph, vesicular, granular , Among them there were also the necrotic tissue infiltrated with cells and lymphocytes seen also with the conclusion Necrobiotic Xanthogranuloma.

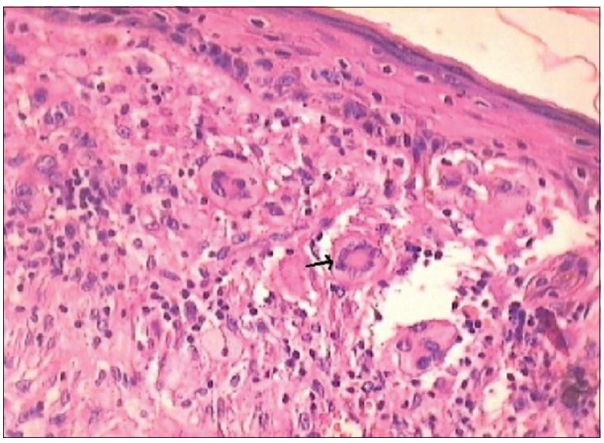

Figure 3. Histopathology FNA

Our management of patients with the administration of cyclosphospamide 6 cycles, as much as 750 mg / m2 / 3 weeks is planned for 6 months. Continued administration of methyl prednisolone tappering off each one month at a dose of 40 mg, 32 mg, 16 mg, 8 mg, 4 mg and

2 mg. Currently the patient is already undergoing a third cycle CYC administration with the result: a thickening in the cheek and the left preaurikuler is not palpable, began to be seen since the second cycle.

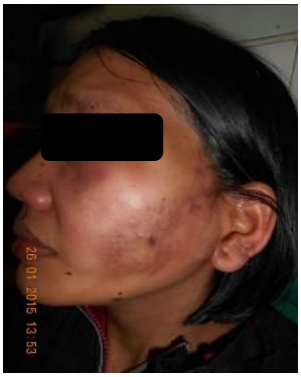

Figure 4. Clinical Pictures Patient Before Giving Cyclosphospamide

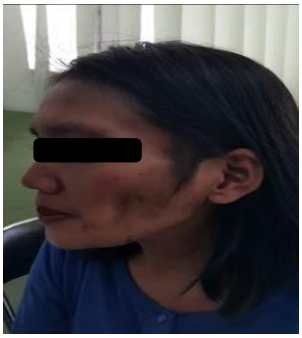

Figure 5. Clinical Pictures Post Cyclosphospamide Sixth Cycle

DISCUSSION

Necrobiotic xanthogranuloma histopathologic picture is similar to xanthogranuloma, such as the presence of foam cells (foamy cells) and touton giant cell and associated with collagen degeneration area, aggregation or lymphoid follicles associated with germinal center, focal plasma cells and cholesterol. NXG and xanthogranuloma about as much in men and women, especially in the decade to 6. Areas affected mainly periorbital, trunk and proximal parts of the extremities. Lesions were first in the form xanthelasma but gradually turns into a brownish yellow indurated plaques with tendency to ulceration and often cause damage to kulit.[1-4]

Under the guidance of experts rheumatology, for use cyclosphospamide (CYC) in inflammation involving dysregulation of B cells, such as lupus nephritis or disease granulomatos autoimmune such as Wegener's granulomatosis and Churg-Strauss syndrome, we then treat patients with a combination of 6-month infusion CYC and methyl prednisolone.

The purpose of this drug combination is rapidly lowering the inflammatory process and the progression of the disease so that it can be maintained results penyembuhannya.[1-4]

Known from various journals, the relationship between NXG with hematological dangerous circumstances (emergency), it is associated with the potential for overlap with periocular Xanthogranuloma With Adult-Onset Asthma (PXAOA). So that the necessary examination of clinical hematology regular full blood count, inflammatory markers and serum proteins elektroporesis.[1-4]

In the discussion of the first case of male patients with NXG we have done with the use of methyl prednisolone treatment with an initial dose of 32 mg and then tappering off for 1 month showed improved outcomes and reduced swelling of the face, and we will continue with the provision of CYC.

In the second case of female patients, we have done the treatment with CYC 750 / m2 are planned for 6 cycles per 3 weeks and underwent 3 cycles, and we combine with methyl prednisolone 0.8 mg / kg / month ago in tappering off showed a very well and his condition improved.

Cyclosphospamide a class of anti-neoplastic alkylating agents are widely used in treating various malignancies case. These compounds work by mengalkilasi nitrogenous bases of DNA of tumor cells so that DNA replication and cell proliferation terhenti.[13]

Methyl prednisolone is an anti-inflammatory that is identical to cortisol, a natural steroid hormone in humans are synthesized and excreted by the adrenal cortex. Anti-inflammatory effects can affect a variety of immunocompetent such as T cells, magrofag, dendritic cells, eosinophils, neutrophils, and mast cells, by inhibiting the inflammatory response and lead to apoptosis of various cells tersebut.[14]

Various library / journal shows the variation of the treatment of NXG especially medical, start giving cyclosphospamide, low-dose chlorambucil, methotrexate, thalidomide, lenalidomid, melpalan, intravenous immunoglobulin, vitamin A, prednisone, dexametason and methyl prednisolone. When the medical management of unsuccessful can proceed with surgery, although the results are less memuaskan.[1,4]

In both cases we get NXG concluded that in addressing the enforcement needs to be a good diagnostic and management of evidence-based NXG. Second case we found is expected to add to their repertoire in the management of NXG.

References

1. Efebera Y. Necrobiotic xanthogranuloma. Clin Adv Hematol Oncol. 2011;9 (9):700–1.
2. Papagoras C, Kitsos G, Voulgari PV, Zikou AK, Argyropoulou MI, Zioga A, et al. Periocular xanthogranuloma:a forgotten entity? *Clinical Ophthalmology.* 2010;*4(1):*105–10.
3. Ryan E, Warren Lj, Szabo F. Necrobiotic xanthogranuloma: response to chlorambucil. Australas J Dermatol. 2012;53(2):23–5.
4. Efebera Y, Blanchard E, Allam C, Han A, Lee S, Munshi N. Complete response to thalidomide and dexamethasone in a patient with necrobiotic xanthogranuloma associated with monoclonal gammopathy a case report and review of the literature. Clin Lymphoma, Myeloma Leuk. 2012;11(3):298–302.
5. Silapunt S, Chon SY. Generalized necrobiotic xanthogranuloma successfully treated with lenalidomide. J Drugs Dermatol. 2010;9(3):273–6.
6. Wood AJ, Wagner MV, Abbott JJ, Gibson LE. Necrobiotic xanthogranuloma: a review of 17 cases with emphasis on clinical and pathologic correlation. Arch Dermatol. 2009;145(3):279–84.
7. Hallermann C, Tittelbach J, Norgauer J, Ziemer M. Successful treatment of necrobiotic xanthogranuloma with intravenous immunoglobulin, *Arch Dermatol.* 2010;146(9):957–60.
8. Fernandez-Herrera J, Pedraz J. Necrobiotic Xanthogranuloma. Semin Cutan Med Surg. 2007;26(2):108–13.
9. Torabian SZ, Fazel N, Knuttle R. Necrobiotic xanthogranuloma treated with chlorambucil. Dermatol Online J. 2006;12(5):11.
10. Chave TA, Chowdhury MM, Holt PJ. Recalcitrant necrobiotic xanthogranuloma responding to pulsed high–dose oral dexamethasone plus maintenance therapy with oral prednisolone. Br J Dermatol. 2001;144(1):158–61.
11. Machado S, Alves R, Lima M, Leal I, Massa A. Cutaneous necrobiotic xanthogranuloma-sucessfully treated with low dose chlorambucil. Eur J Dermatol. 2001;11(5):458–62.
12. Meyer S, Szeimies RM, Landthaler M, Hohenleutner S. Cyclophosphamide–dexamethasone pulsed therapy for treatment of recalcitrant necrobiotic xanthogranuloma with paraproteinemia and ocular involvement. Br J Dermatol; 2005;153(2):443–45.

13. Brundage D. Cancer chemotherapy and treatment. In: Chisolm-Burns MA, Schwinghammer TL, Wells BG, et all, eds. Pharmacotherapy: Principle and Practice. 2nd ed. New York: McGraw-Hill; 2010. p. 1445-74.
14. Smoak KA, Cidloski JA. Glucocorticoid signaling in health and disease. The Hypothalamus-Pituitary-Adrenal Axis; 2008. 33-53.