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Reactive Cutaneous Cytophagocytosis in Nocardiosis

Cutaneous nocardiosis, which usually manifests in the form of pustules, abscesses, or subcutaneous nodules, is occasionally found in immunocompromised patients. A 59-yr-old Korean man with myasthenia gravis and thymoma developed nodular skin lesions on his trunk. Histopathologically, abscess formation with a dense infiltrate of neutrophils and many cytophagic histiocytes were observed. Numerous filamentous organisms, which turned out to be *Nocardia asteroides* by culture, were also found. After sulfamethoxazole-trimethoprim therapy, all of the skin lesions rapidly decreased in size, with a marked diminution of the number of cytophagic histiocytes, and cleared up within four months. On reporting a case of cutaneous nocardiosis showing unusual histopathologic findings, we considered that reactive conditions should be included in the differential diagnosis of the cutaneous cytophagocytosis, and that nocardiosis could be one of the diseases showing reactive cytophagocytosis.

Key Words : *Phagocytosis; Panniculitis; Nocardia asteroides; Immunocompromised Hosts*

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INTRODUCTION

Cytophagocytosis, which is a phenomenon of active phagocytosis of leukocytes, erythrocytes, and platelets by activated histiocytes, can be found in histiocytic diseases and some reactive conditions. Reactive cytophagocytosis has been reported in various malignancies, diphenylhydantoin-induced reaction, and infections. Among the reactive changes due to infections, various bacterial, mycobacterial, rickettsial, viral, fungal, and parasitic infections were reported to induce reactive cytophagocytosis (1). But, there has been no report of reactive cytophagocytosis in nocardiosis. In addition, there have been few reports of reactive cutaneous cytophagocytosis except malignant histiocytosis and cytophagic histiocytic panniculitis in dermatological literature (1, 2). We described a case of nocardiosis showing reactive cytophagocytosis.

CASE REPORT

A 59-yr-old Korean man complained of a sudden appearance of nodular skin lesions and fever. He had been diagnosed as myasthenia gravis and thymoma six years before and had received prednisolone and pyridostigmine after thymectomy. During the therapy, diabetes, hypertension, and onychomycosis occurred. One month prior to his visit, a severe cough with sputum developed. His chest radiography revealed a hazy infiltration in the right middle lung field, but smear and culture of the sputum for acid-fast bacilli (AFB) were negative. Empirical antituberculous medications were administered. However, the fever and more skin lesions occurred and progressed.

Physical examination revealed several subcutaneous nodules on his trunk and proximal extremities, which were erythematous, firm, and tender (Fig. 1). His body temperature was 38.7℃. Laboratory data included a white blood cell count of 20,100/μL with neutrophilia, a hemoglobin level of 10.8 g/dL, and a platelet count of 46,000/μL. The erythrocyte sedimentation rate (ESR) was 42 mm/hr. Serum liver enzyme levels were normal.

Initial pathologic biopsy specimens from the left shoulder lesion showed abscess formation with a dense infiltrate of neutrophils and occasional mononuclear cells (Fig. 2). In addition to neutrophils, numerous histiocytes phagocytizing leukocytes, and erythrocytes were frequently observed (Fig. 3). Many of these histiocytes showing cytophagocytosis were positive for α1-antitrypsin and lysozyme by immunohistochemical stain (Fig. 4). Bone marrow aspirate and biopsy showed a hyperplastic reaction without cytophagocytosis.

We suspected histiocytic cytophagic panniculitis showing unusual clinical features and tried chemotherapy. However, the fever persisted and some of the lesions became suppurat-

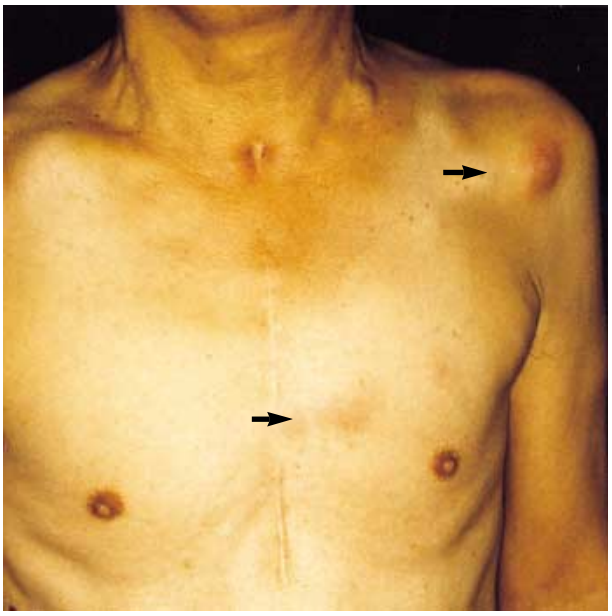

Fig. 1. Two firm, tender, movable, and protruding masses are seen on the patient's left shoulder and anterior chest (arrows).

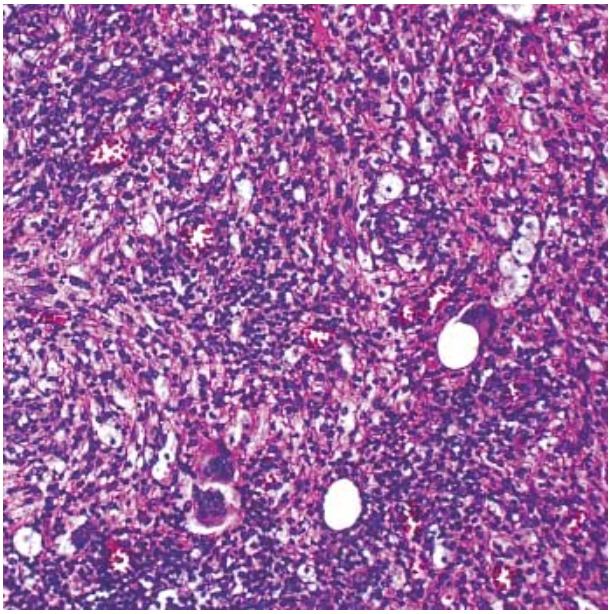

Fig. 2. Neutrophilic abscess formation in dermis and subcutis (Hematoxylin-Eosin stain, × 100).

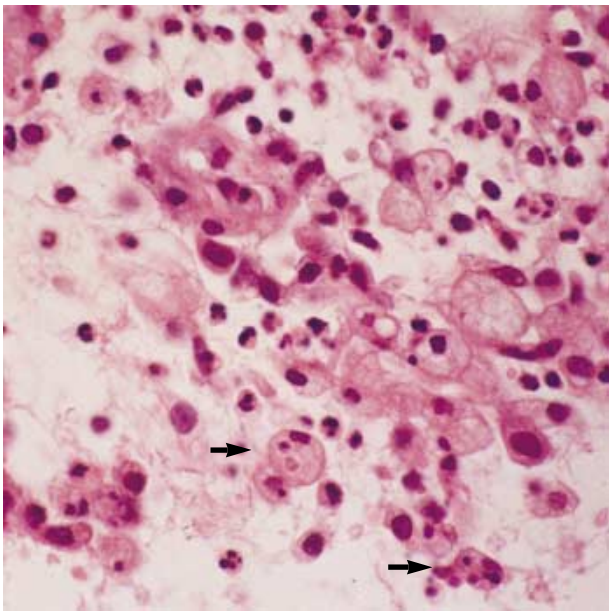

Fig. 3. In addition to neutrophils, numerous histiocytes phagocytizing leukocytes (arrows), and erythrocytes are frequently observed (Hematoxylin-Eosin stain, × 400).

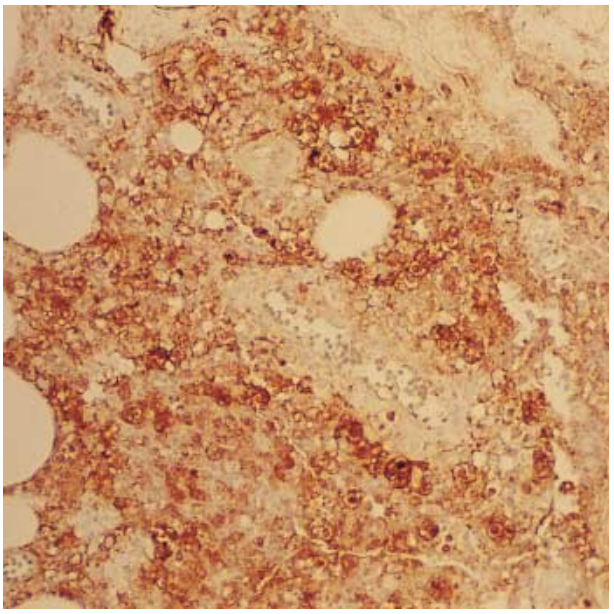

Fig. 4. Many of the histiocytes which are positive for α1-antitrypsin and lysozyme show cytophagocytosis by immunohistochemical stain (× 100).

ed. Aspiration smear and culture of the suppurated lesions showed chalky white colony on blood agar containing many Gram-positive filamentous organisms that is weakly positive for AFB stain. They decomposed urea but not casein, xanthine or tyrosine, and were identified as *Nocardia asteroides.* A pathologic slide of the suppurated lesions revealed numerous filamentous organisms, which were stained positively with Gomori's methenamine silver stain within the abscess, too. Gomori's stain of the initial pathologic slide also revealed many filamentous organisms (Fig. 5). Ultrastructurally, many organisms coated with cell wall were observed within the histiocytes (Fig. 6).

After treatment of sulfamethoxazole-trimethoprim, the skin lesions improved rapidly. Two months later, a biopsied speci-

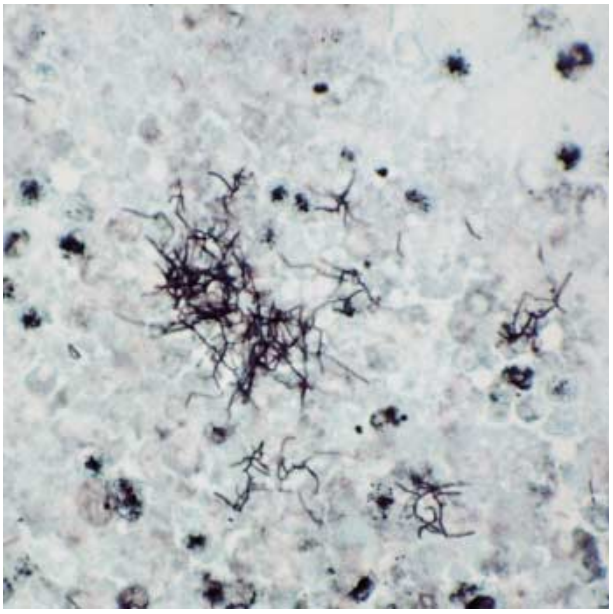

Fig. 5. Groups of aggregated filamentous organisms are distributed in the dermis (Gomori's methenamine silver stain, ×400).

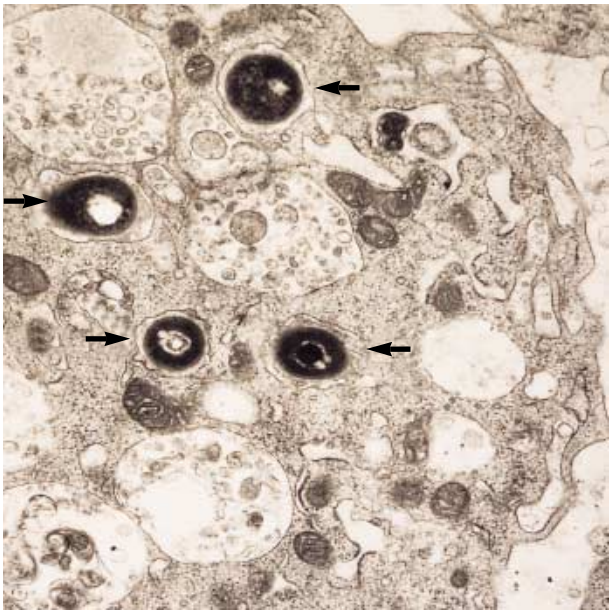

Fig. 6. Ultrastructurally, many organisms coated with cell wall are observed within the histiocytes (arrows) (×8,000).

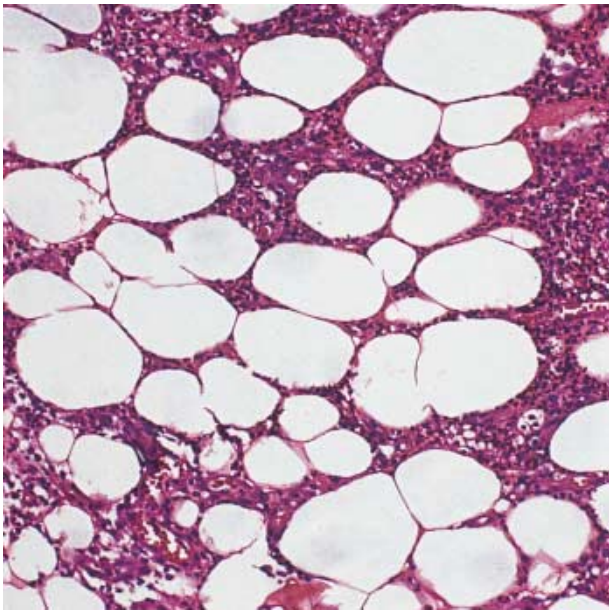

Fig. 7. Two months later, a biopsy specimen from the remainder of the nodules shows granulomatous lesions infiltrated with much decreased neutrophils and only a small number of cytophagic histiocytes (Hematoxylin-Eosin stain, ×100).

men from the remainder of the nodules showed granulomatous infiltrations with much decreased neutrophils and only a few numbers of cytophagic histiocytes (Fig. 7). The skin lesions improved progressively and disappeared completely after four months of antibiotic therapy. The lesions did not recur until he died of myasthenia gravis two months later.

DISCUSSION

Nocardiosis usually occur in immunosuppressed patients such as organ transplant patients (3-5) or patients receiving longstanding immunosuppressants (6, 7). The patient presented also received similar treatment because of thymoma and myasthenia gravis. Although we could not find AFB in his sputum, the cutaneous lesions seemed to be secondarily spread lesions after primary pulmonary nocardiosis. He showed clinical features of pulmonary nocardiosis like fever, severe cough with sputum, hazy infiltration in the right middle lung field in the chest radiography, leukocytosis and elevated sedimentation rate. In addition, his skin lesions occurred as multiple scattered subcutaneous nodules that were erythematous, firm and tender, which is typical for the skin lesions following the primary lung infection. The negative findings in sputum examinations would be due to both the sparseness and the very weak acid-fastness of *N. asteroides* in his sputum. As they are so weakly positive to AFB stain, only modified methods like modified Kinyoun (8) or Fite-Paracco (9) stain will reveal them instead of the ordinary AFB stain we used.

Reactive cutaneous cytophagocytosis seems to be somewhat unfamiliar to many dermatologists and pathologists, and the findings thereof can easily lead to an incorrect diagnosis. Indeed, in spite of the clinical findings such as leukocytosis, increased ESR, and neutrophilic abscess formation, we initially suspected a histiocytic disease.

Cytophagic histiocytic panniculitis is characterized by recurrent episodes of subcutaneous panniculitis, fever, splenomegaly, pancytopenia, abnormal liver function, and terminal hemodynamic instability (1, 2, 10). Histopathologic findings

of histiocytic cytophagic panniculitis usually show subcutaneous panniculitis with an intense histiocytic infiltration and cytophagocytosis of morphologically benign histiocytes (10-12), whereas in malignant histiocytosis, the clinical course is rapid and fatal, and the morphology of the histiocytes is recognizably malignant and atypical (13-15).

Reactive cytophagocytosis due to hidden infections of bacterial, viral, or other organisms can induce similar findings, too (10, 14). In this case, reactive cytophagocytosis could be diagnosed by: firstly, numerous filamentous organisms, which were positively stained by Gomori's stain, were found within the lesions, and they were identified as *N. asteroides*; secondly, the skin lesions improved, and the number of the cytophagic histiocytes decreased after Bactrim® therapy; thirdly, reactive cytophagocytosis was found in cutaneous lesion, but not in bone marrow. It is in accordance with the frequent sites of involvement in nocardiosis, i.e., lung, brain, and skin (16, 17).

The precise mechanism of reactive cytophagocytosis is unclear. Many authors emphasized the association of immunologic abnormalities, particularly of immunosuppression. It is possible that, in immunodeficient state, the elaboration of lymphokines might proceed unchecked and induce activation of macrophages and the resultant cytophagocytosis. The benign appearance of the phagocytic histiocytes suggests that they are reactive in response to circulating cytokines, which may be secreted by activated macrophages and lymphocytes in the focal cutaneous infiltrates. Cytokines implicated in hemocytophagocytic syndrome related to neoplastic lymphocytes include phagocytosis-inducing factor, but cytokines related to benign panniculitis have not yet been identified (18). Among lymphokines, gamma interferon, tumor necrosis factor, and granulocyte monocyte colony stimulating factor were reported to be able to activate macrophages. Other factors that were suspected to have an important role in reactive cytophagocytosis were bacterial sepsis and transfusion, and genetic factors (19). In the present case, the patient had a history of myasthenia gravis with thymoma and long-standing steroid therapy. Many immunologic abnormalities such as decreased humoral and cellular immunity are frequently associated with thymoma. Although it is unclear whether the main etiologic factor is immunologic abnormalities associated with thymoma or long-standing steroid therapy, or still others, it is feasible to suggest that immunologic abnormality might have played an important role in reactive cytophagocytosis.

In summary, we reported a case of cutaneous nocardiosis showing reactive cytophagocytosis in a patient receiving long-standing steroid therapy due to myasthenia gravis with thymoma. We believe that nocardiosis should be included in the differential diagnosis of the disease showing reactive cytophagocytosis.

REFERENCES

1. Winkelmann RK, Bowie EJ. *Hemorrhagic diathesis associated with benign histiocytic, cytophagic panniculitis and systemic histocytosis. Arch Intern Med 1980; 140: 1460-63.*
2. Crotty CP, Winkelmann RK. *Cytophagic histiocytic panniculitis with fever, cytopenia, liver failure and terminal hemorrhagic diathesis. J Am Acad Dermatol 1981; 4: 181-94.*
3. Chae EY, Kim YK, Park EJ, Park JH, Park JH, Yang CW, Kim YS, Bang BK. *A case of empyema thorax and intraabdominal abscess caused by Nocardiae species. Korean J Nephrol 1999; 18: 825-9.*
4. Huh D, Lee JM, Jung YS, Jang ID, Kam BK, Kim MS, Kim JK, Lee SR, Lee JS. *Two cases of Norcardial infection in the renal transplant recipient. J Korean Soc Transplant 1997; 11: 131-5.*
5. Agarwal R, Ayyagari A, Prasad KN, Nag VL, Sharma RK. *Primary subcutaneous Nocardia asteroides infection in a renal allograft recipient. Mycopathologia 1999; 148: 113-5.*
6. Kim HT, Cho WH, Park SB, Kim HC, Chun HJ. *A case of Nocardiosis in renal transplant patient. J Korean Soc Transplant 1996; 10: 151-5.*
7. Oh KW, Kim CS, Song YS, Yang CW, Ahn SJ, Kim YS, Koo WS, Yoon YS, Kang MW, Bang KB. *Trimethoprim/sulfamethoxazole-resistant Nocardiosis in a patient with neprotic syndrome. Korean J Nephrol 1994; 13: 191-5.*
8. McNeil MM, Brown JM. *The medically important aerobic Actinomycetes: Epidemiology and microbiology. Clin Microbiol Rev 1994; 7: 357-417.*
9. Lerner P I. *Nocardia species. In: Principles and practice of infectious diseases. Churchill Livingstone, 1995; 2273-80.*
10. White JW Jr, Winkelmann RK. *Cytophagic histiocytic panniculitis is not always fatal. J Cutan Pathol 1989; 16: 137-44.*
11. Lee JH, Han EH, Kwon KS, Chung TA. *A case of benign cytophagic histiocytic panniculitis. Korean J Dermatol 1994; 32: 99-104.*
12. Lee DW, Park BC, Houh D. *A case of cytophagic histiocytic panniculitis. Ann Dermatol 1990; 3: 133-7.*
13. Chun BN, Shin HJ, Yu HJ, Son SJ. *A case of cytophagic histiocytic panniculitis. Korean J Dermatol 1989; 27: 589-92.*
14. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, Brunning RD. *Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 1979; 44: 993-1002.*
15. Aronson IK, West DP, Variakojis D, Ronan SG, Iossifides I, Zeitz HJ. *Panniculitis associated with cutaneous T cell lymphoma and cytophagic histiocytosis. Br J Dermatol 1985; 112: 87-96.*
16. Shapiro PE, Grossman ME. *Disseminated Nocardia asteroides with pustules. J Am Acad Dermatol 1989; 20: 889-92.*
17. Kalb RE, Kaplan MH, Grossman ME. *Cutaneous nocardiosis. Case reports and review. J Am Acad Dermatol 1985; 13: 125-33.*
18. Stark B, Cohen IJ, Pecht M, Umiel T, Apte RN, Friedman E, Levin S, Vogel R, Schlesinger M, Zaizov R. *Immunologic dysregulation in a patient with familial hemophagocytic lymphohistiocytosis. Cancer 1987; 60: 2629-36.*
19. Horn TD, Hines HC, Farmer ER. *Erythrophagocytosis in the skin: case report. J Cutan Pathol 1988; 15: 399-403.*