Sweet's Syndrome: a Reaction to Non-Tuberculous Mycobacterial Infections

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Sweet's syndrome has been reported to be associated with many underlying conditions; such as non-tuberculous mycobacterial infections (NTMI). In the literature, only twelve patents with Sweet's syndrome in association with NTMI have been reported (most of the patients were from Thailand). Here, the authors report six more patients who developed Sweet's syndrome as a reaction to NTMI. Four patients had Mycobacterium chelonae/abscessus group infection; one patient had been infected with Mycobacterium avium complex first and became infected with M. chelonae/abscessus group 17 months later; and, the other one had Mycobacterium fortuitum infection. In each patient, the skin lesions of Sweet's syndrome relapsed many times while they still had NTMI, and these lesions usually responded well to short courses of systemic steroids without any deterioration of NTMI.

Keywords : *Sweet's syndrome, Dermatosis, neutrophilic, acute febrile, Neutrophilic dermatosis, acute febrile, Mycobacterium chelonae/abscessus, Mycobacterium avium complex, Mycobacterium fortuitum*

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Case reports of Sweet's syndrome were first described in 1964 as an acute febrile neutrophilic dermatosis with four distinctive cardinal features: fever, leukocytosis, painful erythematous plaques and histologically dense dermal infiltrate with mature neutrophils[1]. In 1986, two major and four minor criteria were proposed to be essential for the diagnosis of Sweet's syndrome[2]. The pathogenesis of this syndrome remains unclear. It is thought to be a hypersensitivity reaction to a variety of antigens, and a reaction to immune complex or associated with cytokines[3-8]. Sweet's syndrome has been reported to be associated with many conditions, ie, infection, autoimmune disorders, malignancy, pregnancy or drugs[9-15]. The association with non-tuberculous mycobacterium infections (NTMI) has rarely been reported, so far only twelve cases have been reported, most of them were from Thailand[16-18]. In the present article, six cases of Sweet's syndrome associated with NTMI are described.

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Case Report

The authors undertook a retrospective study of six patients who had Sweet's syndrome concomitant with NTMI at the Department of Medicine, Faculty of Medicine, Ramathibodi Hospital between January 1993 and August 2002. The clinical data were recorded with regard to clinical findings, laboratory investigations, treatment, course of disease, and outcome. The diagnosis of Sweet's syndrome was based on characteristic skin lesions: acute painful, well demarcated erythematous, edematous plaques and, papules or nodules with histopathology of dermal neutrophilic infiltrates without vasculitis. For a definite diagnosis of Sweet's syndrome these patients were required to fulfill two major criteria and, at least, two of the minor criteria as suggested by Su and Liu[2]. Skin lesions were investigated for organisms which included cultures for bacteria, atypical mycobacteria and fungi, and all were negative. The diagnosis of NTMI was based on culture of clinical specimens from sterile sites on mycobacterial media. Other precipitating factors or associated diseases were ruled out, based on the records of history,

physical examinations and laboratory findings in each patient.

Among these six patients, four were female and two were male; their ages ranged from 40-52 years (mean 48 years). The clinical features of these patients are summarized in Table 1. The cutaneous manifestation and histopathology of the skin lesion of patient No.2 is shown in Fig. 1 to 5 respectively. All of these patients had no HIV infection. One patient (No. 3) had diabetes mellitus; other patients had no underlying disease. These patients were followed up from 6 months to 5.4 years.

All of the six patients presented with prolonged fever, malaise, weight loss and cervical lymphadenopathy. Lymph node biopsy revealed granulomatous lymphadenitis. Three patients (No. 4, 5 and 6) also had caseous necrosis of the lymph nodes. Culture of lymph nodes from four patients (No. 1, 2, 5, 6) revealed *Mycobacterium chelonae/abscessus* group. Culture of lymph nodes from patient No. 3 initially revealed *Mycobacterium avium* complex, but 17 months after onset of NTMI, she developed cervical lymphadenopathy again and culture of lymph node revealed *M. chelonae/abscessus* group. Patient No. 4 had *Mycobacterium fortuitum* infection of a cervical lymph node. Patient No. 1 also had multiple osteolytic lesions at the right clavicle and left femur. Patient No. 2 had arthritis of the knees, fingers and toes, he also had hepatomegaly and increased liver enzymes. He developed epitrocheal and inguinal lymphadenopathy while still on antibiotics for treatment of NTMI. CT scan of the abdomen revealed enlargement of the matted aorto-caval nodes at celiac level. Culture of inguinal lymph node revealed *M. chelonae/abscessus* group. Patient No. 3 also had left supraclavicular lymphadenopathy, hepatosplenomegaly and interstitial infiltration of the lower lobes of the lungs which progressed into right pleural effusion

Table 1. Clinical data of 6 patients with Sweet's syndrome and NTMI

Patients No.	Sex and Age	WBC,%N (x1,000/μL)	Abnormal findings in various organs	Organism	Underlying Diseases	Correlation between activity of Sweet's syndrome and NTMI
1	F/48	41.9/N82%	LN, bone	*M. chelonae/ abscessus* group	none	Sweet's syndrome developed 1 year after NTMI, and recurred at 6 months after the first episode of Sweet's syndrome, while she still had NTMI
2	M/40	17.1/N67%	LN, liver, joints	*M. chelonae/ abscessus* group	none	Sweet's syndrome developed 6 weeks after NTMI and recurred six times while he still had NTMI
3	F/46	10.2/N77%	LN, lung, liver, spleen	*M. avium* complex, 17 months later she was infected with *M. chelonae/ abscessus* group	Diabetes mellitus	Sweet's syndrome developed 2 months after NTMI, second episode developed 1.3 years after NTMI, third episode developed 1.5 years after NTMI. The patient still had recurrent NTMI. At 1.7 years after onset of NTMI she had enlargement of cervical lymph nodes again, culture from lymph node revealed *M. chelonae/ abscessus* infection
4	M/49	39.2/N78%	LN	*M. fortuitum*	none	Sweet's syndrome developed 2 months after NTMI and recurred one time while he still had NTMI
5	F/52	10.3/N70%	LN, eyes	*M. chelonae/ abscessus group*	none	Sweet's syndrome developed 2 months after NTMI and recurred six times while she still had NTMI. NTMI was cured after 3 years of treatment
6	F/51	18.7/N79%	LN	*M. chelonae/ abscessus group*	none	Sweet's syndrome developed 6 weeks after NTMI and recurred one time while she still had NTMI

LN = Lymph node, WBC normal 4.0-10.0x1,000/μL; neutrophil normal 40-74%

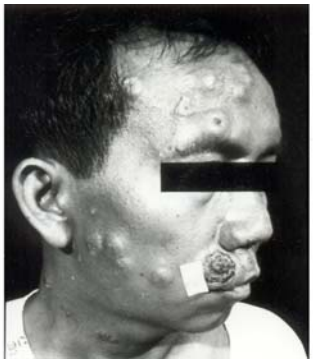

Fig. 1 Erythematous plaques on the face of patient number 2

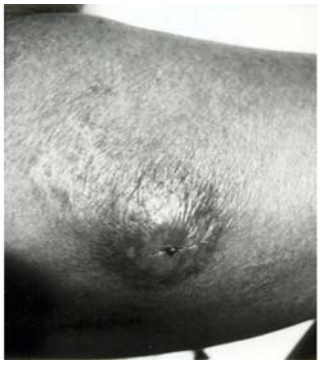

Fig. 2 Erythematous edematous plaque on the arm of patient number 2

Fig. 3 Histopathology of the skin lesion from the trunk of patient number 2. Superficial and deep inflammatory cell infiltrate with neutrophils and nuclear dusts scattered among collagen bundles in edematous dermis. (Hematoxylin-eosin stain, original magnification x 100)

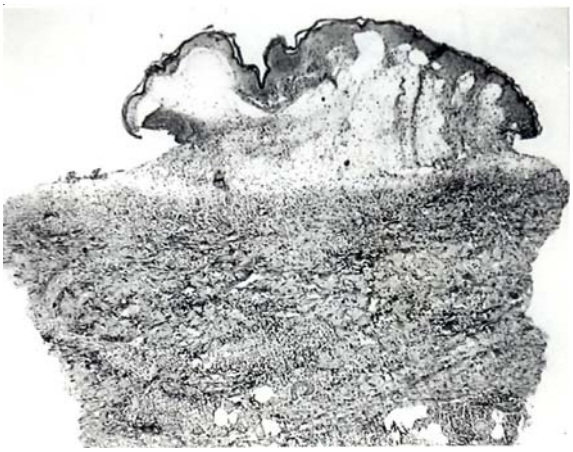

Fig. 4 Histopathology of the skin lesion from the arm of patient number 2. Dense diffuse infiltrate of neutrophils and nuclear dusts throughout upper dermis with edema of papillary dermis (Hematoxylin-eosin stain, original magnification x 100)

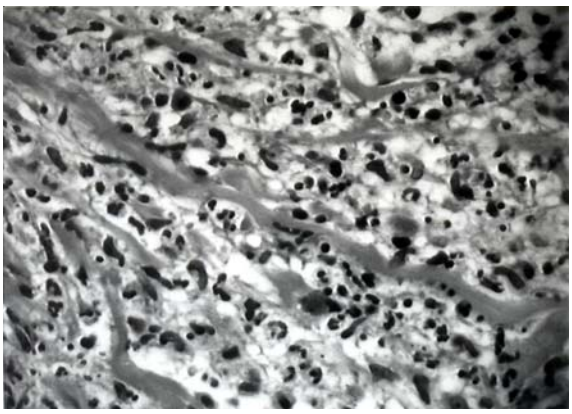

Fig. 5 Histopathology of the skin lesion from the arm of patient number 2. Infiltrate of neutrophils and nuclear dusts in the dermis (Hematoxylin-eosin stain, original magnification x 400)

but the sputum examination was negative for acid-fast bacilli. The chest roentgenogram improved after one year of antibiotic treatment for NTMI. Patient No. 4 had generalized lymphadenopathy, but became lost to follow up 6 months after he had the first episode of Sweet's syndrome. Patient No. 5 had multiple bilateral enlarged cervical lymph nodes and also developed bilateral panuveitis, probably from NTMI. Patient No. 6 had cervical and axillary lymphadenopathy at first and subsequently developed pre-and post-auricular and inguinal lymphadenopathy while she was still on antibiotics for treatment of NTMI.

The initial treatment of these patients included antituberculous drugs (isoniazid, rifampicin, ethambutal, pyrazinamide) while waiting for the result of mycobacterial cultures. After the identification of causative organisms, the antibiotics were changed

according to the susceptibility test. Most of the patients required a prolonged period of treatment with multiple relapses; patient No. 5 was an exception in that the antibiotics could be discontinued after 3 years of treatment, but she still required long term follow-up.

The skin lesions of Sweet's syndrome developed 6 weeks to 1 year after the onset of NTMI. All of the patients had typical lesions of Sweet's syndrome. Two of the patients (No. 2 and No. 5) also had multiple pustules in addition to erythematous, edematous plaques, papules or nodules. These two patients had multiple recurrences of skin lesions while they still had NTMI infection. The culture from pustules yielded no organisms. The skin lesion of Sweet's syndrome in patients No. 1 and No. 4 disappeared after treatment with antimicrobial agents and topical steroids. Patient No. 2 responded well to prednisolone 30 mg/day for 2 weeks at the first episode, for the second to sixth episode he developed pustules in addition to erythematous papules and plaques and the skin lesions responded well to prednisolone 20-30 mg/day and clofazimine 100-200 mg/day. The skin lesions disappeared within 2-6 weeks. The interval between each episode varied from 1 week to 6 months. The skin lesions of patients No. 3 and No. 6 responded well to prednisolone 30 mg/day for 2 weeks. Patient No. 5 responded well to colchicine (0.6 mg) twice a day for the first four episodes. However, at the fifth and sixth episodes she developed multiple pustules in addition to erythematous papules and plaques; these skin lesions disappeared after treatment with dapsone 100 mg/day and clofazimine 100 mg/day. The skin lesions healed within 1-2 months. The interval between each episode varied from 2 to 8 weeks. In all the patients who were treated with a short course of prednisolone, the NTMI did not get worse because prednisolone was administered for only 2 weeks intermittently.

Discussion

Sweet's syndrome or acute febrile neutrophilic dermatosis characterized by clinically acute tender erythematous or violaceous plaques or nodules, may appear as papules, pustules or hemorrhagic bullae[3,19]. Histopathology reveals dense dermal infiltrate with neutrophils without leukocytoclastic vasculitis. There is also fever, leukocytosis and good response to systemic steroids[2]. Sweet's syndrome can be associated with many conditions[9-15], but the association with NTMI is quite rare.

Table 2 shows 12 patients reported previously in the English literature, who developed Sweet's syndrome in association with NTMI. In the present study, the authors reported six patients who developed Sweet's syndrome in association with NTMI. All of them had typical skin lesions and characteristic histological features of Sweet's syndrome and culture from the skin lesions of Sweet's syndrome revealed no organism. The atypical mycobacterium found in the present study were *M. chelonae/abscessus* groups in 4 patients, *M. fortuitum* in one patient; the other had infection with both *M. avium* complex and *M. chelonae/abscessus* group. Most of the reported cases of Sweet's syndrome associated with NTMI were from Thailand (11 of 12 cases). The exact incidence of NTMI in Thailand is not known, there is no report about the epidemiology of NTMI in Thailand or other Southeast Asian countries. Five of six patients reported here had no underlying disease, only one patient had diabetes mellitus which may predispose the patient to develop infection. All of the patients presented initially with cervical lymphadenopathy. Sweet's syndrome usually develops after onset of NTMI and recurs many times while the patients still have NTMI infection. The skin lesions of Sweet's syndrome usually respond well to topical or systemic steroids. In one patient the skin lesions disappeared after treatment with colchicine. In two patients who also developed sterile pustules, the skin lesions responded well to clofazimine and dapsone.

In conclusion, six patients with Sweet's syndrome associated with NTMI were reported. The organisms responsible for the infection included the *M. chelonae/abscessus* group, *M. fortuitum* and *M. avium* complex. The skin lesions of Sweet's syndrome developed 6 weeks to one year after the onset of NTMI and recurred many times while the patients were still infected with NTMI. In most patients, the skin lesions responded well to topical or systemic steroids. The course of NTMI was prolonged and difficult to treat, only one patient seemed to be cured after 3 years of treatment.

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Table 2. Findings in 12 patients with Sweet's syndrome and NTMI

	Sex and Age	Abnormal findings in various organs	WBC,%N (x1,000/μL)	Organism	Correlation between activity of Sweet's syndrome and NTMI
Choonhakarn C, et al[16]	F/39	LN, bone, breast, liver, spleen, sinus	24.8/89%	*M. chelonae*	Sweet's syndrome developed at second episode of recurrent NTMI
	F/30	LN, bone	18.7/77%	*M. scrofulaceum*	Sweet's syndrome developed at the same time as NTMI
	F/41	LN, Guillain-Barre' syndrome	36.2/77%	*M. chelonae*	Sweet's syndrome developed at the same time of NTMI
	M/25	LN, joint, liver, spleen	12.0/82%	*M.avium* complex	Sweet's syndrome developed at the same time as NTMI
	M/35	LN, lung, brain stem	25.8/88%	*M. chelonae*	Sweet's syndrome developed at the same time of NTMI
Hsiao GH, et al[17]	F/25	LN, lung	13.7	*M. fortuitum*	Sweet's syndrome developed 5 months before NTMI and recurred again in concomitant with recurrent NTMI. Skin lesions disappeared after successful treatment of NTMI
Chetchotisakd P, et al[18]	F/38	The same patients as reported by Choonhakarn[16]			
	M/35	The same patients as reported by Choonhakarn[16]			
	F/41	The same patients as reported by Choonhakarn[16]			
	F/31	LN, sinus, liver	24.8	M. *abscessus*	Not mentioned
	F/41	LN, sinus, liver, spleen	21	M. *abscessus*	Not mentioned
	F/36	LN, lung	35.7	*M. abscessus*	Not mentioned
	M/55	LN, lung	14.7	*M. abscessus*	Not mentioned
	M/47	LN, sinus	22.2	*M. abscessus*	Not mentioned
	M/51	LN	29.5	*M. abscessus*	Not mentioned

LN = Lymph node

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Sweet's syndrome: ปฏิกิริยาที่เกิดจากการติดเชื้อ mycobacteria ที่ไม่ใช่เชื้อวัณโรค

ชนิษฎา ตู้จินดา, ศิริเพ็ญ พัววิไล, บุญมี สถาปัตยวงศ์, สมนึก สังฆานุภาพ, อัษฎา วิภากุล, สุเทพ จิระสุทัศน์, ณัฏฐา รัชตะนาวิน, เพ็ญวดี ทิมพัฒนพงศ์

มีรายงานว่า Sweet's syndrome สามารถเกิดร่วมกับโรคต่าง ๆ ได้หลายชนิด เคยมีรายงานการเกิด Sweet's syndrome ร่วมกับการติดเชื้อ mycobacteria ที่ไม่ใช่เชื้อวัณโรคมาแล้ว 12 ราย ซึ่งส่วนใหญ่เป็นรายงานผู้ป่วยจากประเทศไทย ในรายงานนี้ได้เสนอผู้ป่วยอีก 6 ราย ซึ่งมี Sweet's syndrome เกิดขึ้นเป็นปฏิกิริยาต่อการติดเชื้อ mycobacteria ที่ไม่ใช่เชื้อวัณโรค ผู้ป่วย 4 รายติดเชื้อกลุ่ม Mycobacterium chelonae/abscessus ผู้ป่วย 1 รายติดเชื้อ Mycobacterium avium complex ก่อนแล้วหลังจากนั้น 17 เดือน เกิดติดเชื้อกลุ่ม M.chelonae/abscessus อีก ผู้ป่วยอีก 1 รายติดเชื้อ Mycobacterium fortuitum ในผู้ป่วยแต่ละรายเกิดรอยโรคของ Sweet's syndrome หลายครั้ง ในขณะที่ยังติดเชื้อ mycobacterium อยู่ และรอยโรคของ Sweet's syndrome ยุบหายดี หลังจากรักษาด้วยยาสตีรอยด์ชนิดรับประทานเป็นระยะเวลาสั้น ๆ โดยไม่ทำให้การติดเชื้อ mycobacteria มีอาการมากขึ้น