

LETTERS TO THE EDITOR

Sweet's Syndrome and Erythema Nodosum after *Klebsiella pneumoniae* Cystitis

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Accepted February 5, 2003.

Sir,

We read with interest the paper by Carpentier et al. in *Acta DermatoVenereologica* (1) reporting a case of Sweet syndrome (SS) following BCG vaccination – the authors hypothesizing that SS could be an abnormal immunological reaction to a variety of antigens.

On this topic, molecular mimicry has been proposed as a pathogenic mechanism for autoimmune and reactive skin diseases, as well as a probe useful for uncovering their aetiologic agents. Increasing clinical and experimental evidence suggests the possible association of infectious agents with autoimmune diseases, and cross-reactivity between host self-antigens and microbial determinants has also been observed. Infecting pathogens, in fact, express peptides that are similar in structure and sequence to particular self-components, and this induces immune responses between pathogen and host (2, 3).

We describe a peculiar presentation of SS and erythema nodosum (EN) with almost simultaneous occurrence of urinary tract infection disease caused by *Klebsiella pneumoniae*, raising the possibility that this bacterium might trigger the clinical appearance of the reactive diseases.

CASE REPORT

A 34-year-old woman was referred to our department with a 10-day history of extensive, painful eruption involving her face and extremities, accompanied by mild fever, recurrent cephalgia and arthralgia. Clinical examination revealed two erythematous-infiltrative, well-demarcated and approximately round, red-violet plaques measuring about 2–3 cm in diameter, localized on the face; similar tender erythematous-edematous plaques on the pretibial area of both legs were also present. The patient referred symptoms of a urinary tract infection.

Clinical history revealed that about 2 months prior to the appearance of the skin lesions an acute cystitis had developed and was improved by antibiotic therapy. Laboratory blood tests revealed a white blood cell count of 13100/mm³ with neutrophilia (80%), erythrocyte sedimentation rate elevated at 65 mm in the first hour and at 103 mm in the second hour, decreased haemoglobin (11.4 g/dl), haematocrit (32.4%) and mean corpuscular volume (81 micron³), C-reactive protein at 320 mg/l (normal value 0.0–5.0 mg/l) and antistreptolysin-O titres at 300 IU/ml (normal value ≤200 IU/ml). Serum electrophoresis showed increased α_1 and α_2 fractions (4.6% and 16.2%, respectively; normal values

1.4–4.0% and 9.0–14.0%) and decreased albumin, at 46.4% (normal value 52.0–66.0%). A search for a number of serum autoantibodies (antinuclear, anti-ENA, anti JO1 and anti Scl70) was negative.

Emphysematous cystitis was diagnosed based on computed tomographic scanning (showing pockets of air in the bladder lumen surrounding urine in the mildly distended bladder) and urinalysis evidence of the causative agent *K. pneumoniae* (10⁶ cfu of bacteria/ml).

Microscopic evaluation of a biopsy specimen from a frontal plaque showed a normal epidermis, intense infiltrate of mature neutrophils in the mid and upper dermis, leucocytoclasia without overt vasculitic changes. A skin biopsy specimen obtained from the plaque on the right leg showed an inflammatory infiltrate including lymphocytes, histiocytes and macrophages, with neutrophils and multinucleated giant cells in the fibrous septa of subcutaneous adipose tissue; leucocytoclastic vasculitis was absent.

A diagnosis of SS and EN together with *K. pneumoniae* cystitis was made on the basis of the clinical and histopathological picture along with the laboratory and radiological findings. A search for clinical and laboratory signs of diseases reported in association with SS and EN (e.g. Crohn's disease, ulcerative colitis, malignant neoplasms, sarcoidosis) was negative. Our patient was not pregnant and was not taking oral contraceptives or other drugs.

Treatment with oral prednisolone 30 mg daily and antibiotics (a 7-day course of ampicillin and a 3-day course of gentamycin) was then started, with progressive improvement of the cutaneous manifestations. Prednisolone was tapered off and stopped within 3 weeks. The patient is now healthy after 4 months of follow-up and no maintenance treatment was required.

DISCUSSION

The present report describes a case of SS and EN associated with *K. pneumoniae* cystitis and suggests the possible role of the molecular mimicry in the simultaneous occurrence of SS and EN. Only 14 biopsy-proven cases in which both reactive dermatoses presented together are reported in association with a wide variety of systemic conditions involving bacteria, virus, fungi and parasites (4, 5). Despite the common link between SS, EN and infections, to our knowledge there are no reports of their association in patients with urinary tract infection diseases.

SS and EN are chronic inflammatory reactive

disorders of unknown cause and incompletely characterized pathogenesis, although an interplay between genetic and environmental factors, including infections, is likely to occur. A number of recent reports have linked *K. pneumoniae* with autoimmune phenomena: it shares sequence homology with HLA-B27, bacterial DNA was detected in synovial fluid of arthritis patients, high levels of *K. pneumoniae* specific antibodies were found in patients with autoimmune diseases (and possibly by idiotypic cross-reaction triggering autoantibodies), and finally *K. pneumoniae* O3 lipopolysaccharides proven to be a potent immunological adjuvant in the induction of several autoimmune disorders in mouse models (6).

Infection agents may act as triggers of skin reactive diseases via either direct damage or molecular mimicry because of amino acid sequence homologies between microbiological proteins and skin component with subsequent activation of autoreactive T-lymphocytes. This is a necessary first step, but genetic susceptibility, clonal expansion of autoreactive T-cells, induction of a functional phenotype (i.e. cytokine profile) and constitutive expression of major histocompatibility complex molecules and co-stimulatory molecules in the target organ are also required for the development of reactive diseases (3). In SS, elevated serum levels of Th1 type cytokines (IL-1 α , IL-1 β , IL-2, IFN- γ) were found, perhaps as a consequence of an abnormal response to excessive production of IL-1, suggesting an involvement of these substances in the pathogenesis of the disease (7).

Infectious agents can up-regulate Th1 cytokines, thereby increasing selected expression of molecules such as major histocompatibility complex glycoproteins, as well as activation and co-stimulatory molecules leading to imbalance in the immune response (2). These events were observed in several studies on the aetiopathogenesis of

SS and EN (7, 8), suggesting that infectious agents could determine the development of SS and EN through molecular mimicry.

In conclusion, although it is likely that genetically predisposed subjects can develop an abnormal immune response upon contact with an antigen that mimics a self protein, to date, compelling evidence that molecular mimicry is a mechanism for the induction of autoimmunity is available only for a limited number of diseases. The progress made in the identification of microbial peptides, along with a better understanding of the epidemiology of infectious agents and the autoimmunity, will allow a better comprehension of the molecular mechanisms triggering autoimmune diseases.

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