

CLINICAL REPORT

Neopterin and C-Reactive Protein in the Course of Stevens-Johnson Syndrome: Report of a Case

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We describe a patient originally suffering from a depressive syndrome who developed Stevens-Johnson syndrome after 12 days of treatment with lamotrigine. The clinical symptoms and the inflammation parameters neopterin and C-reactive protein were documented. Neopterin values showed a good correlation with the course of the disease, which, to the best of our knowledge, has not been reported previously. C-reactive protein followed the neopterin curve with a delay of 4 days. Since neopterin is a widely available parameter it should be considered as a routine measurement in this type of hyperergic reaction. It might help to identify the beginning, the maximum and the regression of the disease in order to support therapeutic decisions. Key words: Stevens-Johnson syndrome; toxic epidermal necrolysis; neopterin; C-reactive protein; inflammation marker.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe hypersensitivity reactions involving the skin (1). The characteristic symptoms are erythema with a variable extension of detachment and erosions of epidermis and mucous membranes. It is widely accepted that SJS and TEN differ mainly in the extent of the affected skin area (1, 2). Both diseases have a high mortality (25–30%) (1, 3).

More than 90% of SJS/TEN cases occur during the first 2 months of drug intake (1, 4). Certain anti-epileptic drugs are associated with an increased risk of developing SJS/TEN (5–8) specified with a prevalence of a few cases in 10,000 new users (4). Parameters monitoring the course of these diseases could help with therapeutic decisions and scientific evaluations. We describe here a case of SJS caused by lamotrigine in which the disease activity was monitored by measuring the serum levels of neopterin (NPT) and C-reactive protein (CRP). Chemically NPT belongs to the group of pteridines (9). It

is synthesized by monocyte-derived macrophages and dendritic cells upon activation by Th1-type cytokine interferon-gamma (10, 11). NPT is a robust marker to quantify the intensity of cell-mediated immune response. First, it is stable in biological fluids, biochemically inert and the half-life in the human circulating system depends only upon the renal excretion (12). Secondly, the NPT values do not reflect the effect of any single cytokine, but rather indicate the sum of forward and backward immunoregulatory pathways on the monocyte population. Numerous studies have demonstrated a strong correlation between NPT levels and the severity, progression and outcome of infections, inflammatory diseases, allograft rejections and malignancies (13, 14). To our knowledge NPT measurements in SJS/TEN patients have not been reported previously. CRP belongs to the class of acute phase proteins. Conditions that lead to increased serum levels of CRP include acute infections, systemic inflammations of the body, trauma, surgery, burns and advanced cancer. CRP has been found to be significantly increased in SJS/TEN patients (15).

CASE REPORT

A 62-year-old woman was admitted to our hospital because of severe depression. No internal or neurological symptoms were present on admission. The routine blood parameters were normal. Her height was 174 cm and weight 73 kg. The medical history included hypothyroidism, migraine, arterial hypertension and an allergy to sticking plaster.

She was administered 100 mg sertraline daily, resulting in a steady-state serum concentration of 14 ng/ml sertraline and 43 ng/ml desmethylsertraline. A 15 mg dose of mirtazapine was given in the evening to initiate sleep. After 3.5 weeks of this treatment regime the patient's condition had improved but was not in remission. A 25 mg dose of lamotrigine was added daily as an augmentative strategy. Twelve days thereafter she felt flu-like and developed a temperature of 38.2°C. All medication was discontinued. The next day her trunk turned slightly red and the fever was 38.3°C (day 0 in Fig. 1). The following morning she started shivering, complained of a sore throat and the fever rose to 39.1°C

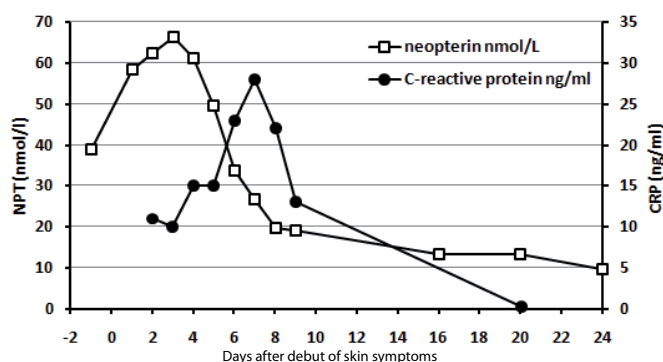


Fig. 1. Serum concentrations of neopterin (NPT) and C-reactive protein (CRP) in a patient with Stevens-Johnson syndrome (SJS). The skin reaction started slightly on day 0 and reached its maximum (80% confluent exanthema and incipient bullae) between days 2 and 4. The general symptoms started on day -1 and peaked on day 1.

(day 1 in Fig. 1). Clinically she now suffered from a stomatitis and a generalized erythematous, maculopapular and confluent exanthema emphasizing the trunk and comprising about 80% of the total body surface area. Another day later (day 2 in Fig. 1) parts of the affected skin detached and formed bullae. Her body temperature returned to normal.

The diagnosis of SJS was supported by skin biopsy and was later confirmed in a second independent histopathological examination (Fig. 2). The patient was examined by an authorized investigator of the European Register for Severe Cutaneous Adverse Reactions (RegiSCAR) and the clinical diagnosis was approved by an expert committee blinded for potential causes. Based on clinical data and histopathology, the case was validated as a "definite" case of SJS. Lamotrigine was considered most likely to be the causal agent.

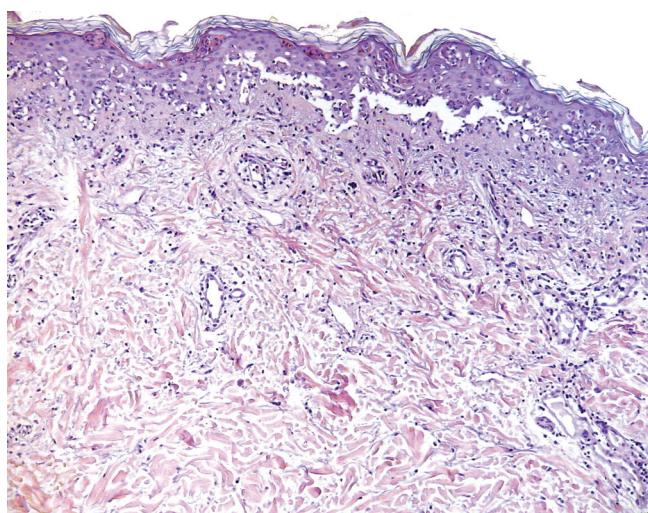


Fig. 2. Histopathology of the patient's skin biopsy: necrotic keratinocytes within the entire epidermis and vacuolar degeneration at the dermal-epidermal junction resulting in subepidermal separation of the epidermis. Sparse superficial lymphocytic infiltrate (haematoxylin and eosin (H&E), original magnification $\times 100$).

Sertraline and mirtazapine were mentioned as possible concomitant causes.

The leukocyte count was depressed during the acute phase of the disease with a minimum of $1.6 \times 10^3/l$ (normal 3.8–10.9) on day 2. The ophthalmological finding was regular. IgM virus serologies for measles, parvovirus, rubella, varicella zoster virus, cytomegalovirus, Epstein Barr-virus, hepatitis B and C virus, *Borrelia burgdorferi* and enterovirus were negative. HIV1-RNA was negative. The sepsis marker procalcitonin was measured daily between day 2 and 5, interleukin-6 on day 1. All values were within normal ranges.

The patient was admitted to the burn centre and kept in protective isolation. She received topical therapy with corticoid ointment and intravenous immunoglobulin treatment (37.5 g/24 h over 3 days). Her condition improved slowly but continuously and she was discharged back to our department 2.5 weeks later. Overall she recovered fully without any consequential damage. Various inflammation markers, especially CRP and NPT, were closely monitored in parallel to the clinical course starting on the day of flu-like symptoms and fever (day -1 in Fig. 1).

NPT serum concentrations were measured by enzyme-linked radio-immunoassay (Brahms AG, Berlin, Germany). Values below 10 nmol/l are regarded as normal.

CRP was measured by a latex-enhanced turbidimetric immunoassay (Tina Quant assay/Roche Diagnostics GmbH, Mannheim, Germany). The range below 5 ng/ml was considered normal.

DISCUSSION

As often described in the literature (4–8), our patient first had unspecific general symptoms, such as fever (day -1), which peaked one day after the first cutaneous signs had appeared (day 1). The dermatological symptoms reached their maximum between one and three days later (days 2–4).

On the day before the skin reaction, NPT had already increased four-fold compared with the normal range (day -1 in Fig. 1). On day 3, NPT reached its maximum with a 5.5-fold increase and then decreased rapidly to values below the double normal range (days 8–9 in Fig. 1). Thereafter the serum levels stabilized near the upper normal limit.

The CRP measurements (≤ 30 ng/ml) were within the range presented by Czelej et al. (15) in previous cases of severe drug reactions. On day 2 the value was increased two-fold, reached its maximum on day 7 and returned to normal before day 20. Interleukin-6 was within normal range on day 1 (data not shown). The same was found for daily measurements of the procalcitonin levels between days 2 and 5 (data not shown).

The course of the NPT measurements was ahead of CRP by some 4 days and was a better reflection of the clinical parameters than the CRP. This time shift can be

observed between day 2 and 9 in Fig. 1. On day 2, NPT was already elevated six-fold in comparison with the upper normal limit, while CRP was increased only two-fold. On day 7, NPT had already returned to 2.5-fold of the upper normal range, while CRP had just peaked.

According to our present knowledge cytotoxic T cells mediate the pathophysiology in SJS by inducing apoptosis in keratinocytes (3, 16). Necrotic keratinocytes lead to the detachment of the skin and the development of bullae. Once triggered, the apoptosis cannot be reversed. Therefore immediate discontinuation of the offending drug is crucial for the prognosis of the patient. At the same time the activated T cells may initiate the production of NPT by stimulation of macrophages and/or dendritic cells. This common pathway might be responsible for the early NPT response and the close relationship between the NPT curve and the clinical course that was observed in our patient.

CRP, on the other hand, is triggered by tissue lesions and inflammatory processes. It therefore rises steeply after the skin reaction has reached its maximum 4 days after the first cutaneous signs had appeared.

We propose that NPT should be monitored in SJS/TEN patient as a possible diagnostic and prognostic factor and marker for therapeutic efficacy.

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