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CASE REPORT

Toxic epidermal necrolysis after linezolid administration: Case report

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ABSTRACT

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are severe skin reactions characterised by epidermal necrolysis. Skin reactions develop as a result of drug induced keratinocyte apoptosis. Certain drugs, like nonsteroidal anti-inflammatory agents, antimicrobial substances and anticonvulsants, cause TEN or SJS more frequently. We present the case of a fatal adverse cutaneous reaction after linezolid administration in a 66-year old patient with severe staphylococcal pneumonia during treatment in the intensive care unit. According to data from the National Agency for Medicinal Products and Medical Devices of Croatia (HALMED), TEN is a rare, but not an unexpected, side effect of this antimicrobial drug. Time of occurrence, distribution and the extent of skin lesions are not typical of TEN, but the result of the postmortal skin biopsy clearly indicates the cause of the reaction.

Key words: epidermal necrolysis, toxic, linezolid, drug-related side effects and adverse reaction

Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are severe skin reactions characterized by epidermal necrosis. Mucous membranes of the respiratory, digestive and urogenital systems can also be affected by necrolysis. Assumingly, a skin reaction develops as a result of drug induced keratinocyte apoptosis in over 80% of all cases. Skin changes appear with a latency of a few days or weeks from administration of the causative agent. Certain drugs like nonsteroidal anti-inflammatory agents, antimicrobial substances and anticonvulsants cause TEN or SJS more frequently. Among chemically related substances a cross reaction is possible. Treatment outcomes depend on the patient's premorbid condition and the percentage of affected skin surface. Death as an outcome is possible in 30% of all patients. (1-4) We present a case of fatal adverse cutaneous reaction after linezolid administration in a patient with severe staphylococcal pneumonia during treatment in the intensive care unit.

Case presentation

A 66-year-old patient was admitted to our intensive care unit (ICU) following after an urgent craniotomy for a spontaneous hypertensive cerebral haematoma (preoperative Glasgow Coma Score 10). His medical history showed that he had chronic obstructive pulmonary disease (COPD) and psoriasis, a penicillin allergy, and was also a smoker and a chronic alcoholic. Preoperative microbiological analysis of tracheal aspirate showed colonization with methicillin resistant Staphylococcus aureus (MRSA). In the early postoperative period, the patient was conscious, with normal breathing and diuresis. An infectious complication developed during the 7th postoperative day, which aggravated the patient's clinical condition. Treatment with vancomycin and meropenem was started, due to the suspicion of postoperative meningitis. The latter was not confirmed, but massive bilateral pneumonia was later established. MRSA and Acinetobacter baummani were isolated from tracheal aspirate. Despite appropriate antimicrobial therapy, the patient's condition did not improve, clinical and laboratory parameters indicated sepsis with initial signs of organ dysfunction (hypotension, azotaemia, deterioration of respiratory function). MRSA was isolated repeatedly from the tracheal aspirate. After three weeks of unsuccessful administration of vancomycin, linezolid was introduced. Six hours after the first dose (600 mg), a purpuric eruption appeared on the extensor surface of both

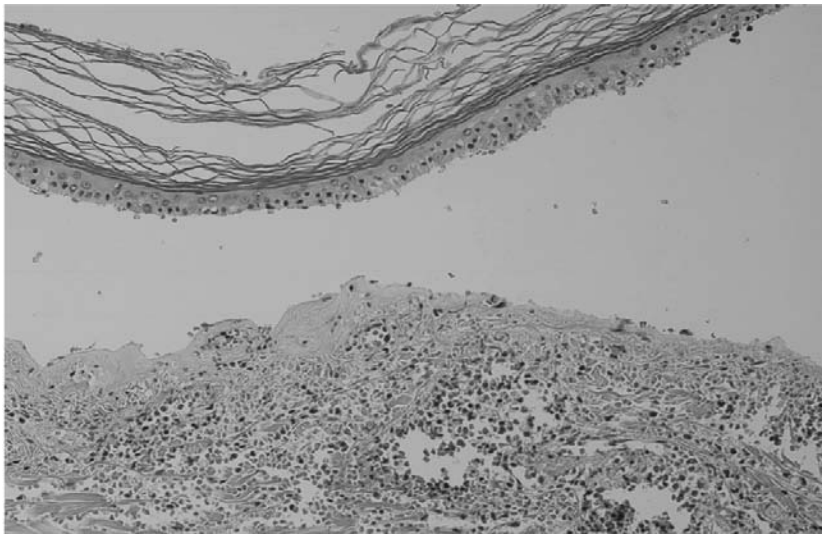

Figure 1a. Confluent necrosis of epidermis with subepidermal bulla and lymphocytic and hystiocytic infiltration within the dermis (HE, 200X).

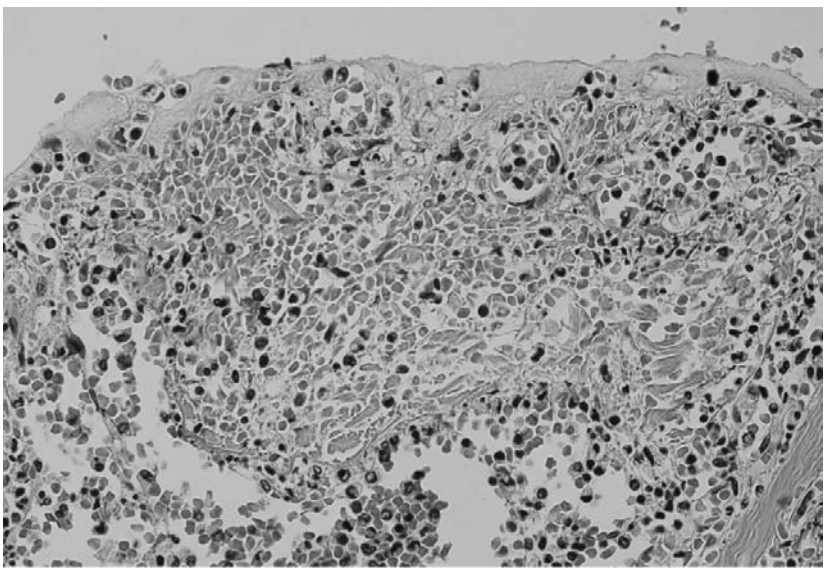

Figure 1b. Medium thick lymphocytic and hystiocytic infiltration within the dermis (HE, 400x).

arms and legs. These petechial lesions were considered a manifestation of sepsis. After the second dose of linezolid, numerous confluent purpuric macules, bullae and erosions appeared in place of the earlier petechial eruption. These changes affected about 10% of the body surface area. The patient's general condition deteriorated dramatically, with clinical signs of progressive organ failure (circulatory shock, anuria, deep coma). Due to suspicion that the skin lesions were related to linezolid treatment, it was omitted from further therapy. Despite the intensive therapeutic measures (mechanical ventilation, vasoactive support, haemodialysis) the patient died three days later. Family members opposed autopsy, so it was not performed, but a postmortal skin biopsy was approved. The result of the skin biopsy suggested toxic epidermal necrolysis (figure 1). The incident was reported to the National Agency for Medicinal Products and Medical Devices of Croatia (HALMED) as a possible side effect of linezolid.

Discussion

The very short latency from linezolid administration to skin eruption and the distribution of the skin changes in our patient are not typical of TEN or SJS. These changes resembled the appearance caused by vasculitis or erythema multiforme. (1-3) No consideration was given to the mucous membrane changes, nor was an autopsy performed which could have shown noticeable internal organ changes characteristic of epidermolytic syndrome. Skin biopsy results exclude the possibility of vasculitis or staphylococcus scaled skin syndrome, and refers to TEN or rather SJS (figure 1). (3,4) A prominent deterioration of the patients' clinical condition after the second drug dose was administered raised doubts about linezolid possibly being the cause, or at least the contributing factor, of the severe skin reaction. According to the HALMED report, TEN is not an unexpected and unintended effect of linezolid and can occur in 0.01 to 0.1% of cases. It should be noted that the patient was simultaneously treated with several other drugs which could potentially cause TEN or SJS, including meropenem, vancomycin and esomeprazole. However, he had been treated with these drugs previously without appearance of any cutaneous reaction. Vancomycin was excluded just before the linezolid introduction. The latter was omitted from further therapy after the clinical deterioration, and administration of meropenem and esomeprazole was continued. It is not possible to exclude one of the stated drugs as the cause of the adverse reaction, which was clinically evident immediately after linezolid inclusion, or even the possibility of cross sensitivity to those drugs. It is presumed that in this case linezolid could have caused or triggered TEN, but the patient's premorbid condition (psoriasis, allergic diathesis, infection) could have contributed to the occurrence and the fatal outcome of the skin reaction. (5)

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