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A Fatal Case of Sulindac-induced Lyell Syndrome (Toxic Epidermal Necrolysis)

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Summary. A 37-year-old woman died after 18 days from her starting to take sulindac for low back pain. Based on her clinical course and the autopsy findings, the cause of her death was Lyell syndrome (toxic epidermal necrolysis) induced by sulindac. This case is described together with the legal aspects of medical malpractice to which it gave rise.

Key words: Sulindac, Lyell syndrome – Toxic epidermal necrolysis – Lyell syndrome

Zusammenfassung. Eine 37jährige Frau starb 18 Tage nach Beginn einer Therapie mit Sulindac, das wegen Schmerzen in der Lendengegend verordnet worden war. Das Krankheitsbild und die Sektionsbefunde sprechen dafür, daß das den Tod verursachende Lyell-Syndrom (Epidermolysis acuta toxica) durch Sulindac ausgelöst worden ist. Es wird im Rahmen der Beschreibung von Verlauf und Befunden die Frage eines ärztlichen Fehlverhaltens (Kunstfehler) angesprochen.

Schlüsselwörter: Sulindac, Lyell-Syndrom – Lyell-Syndrom – Epidermolysis acuta toxica, Therapie mit Sulindac

The Lyell syndrome (toxic epidermal necrolysis) has gained forensic importance because the changes of skin have an extreme likeness with those of a 2nd degree scald [1]. As this illness is more frequently observed as drug allergy, it may get forensic importance from the view point of medical malpractice.

Sulindac (Clinoril; Merck, Sharp, and Dohme), a substituted indene acetic acid structurally related to indomethacine, is a member of the new class of non-steroidal anti-inflammatory agents. Early clinical studies of this drug indicated the occurrence of only relatively mild adverse reactions. However, during post-marketing clinical experience, several serious adverse effects including Lyell

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syndrome, Stevens-Johnson syndrome and hepatotoxicity have been recognized [2–5]. We report an autopsy case who had a fatal outcome after development of the features of Lyell syndrome during sulindac therapy, in which the medical malpractice was suspected.

Case Report

A 37-year-old woman was hospitalized with fever, severe abdominal pain, and a generalized rash. Fifteen days earlier, her surgeon had prescribed 100 mg sulindac three times daily for low back pain. Seven days prior to admission, she developed slight fever, but sulindac therapy was continued. Four days prior to admission, she had an illness consisting of high fever and chills, and subsequently she noted neck and facial erythema on the next day. She was treated empirically by a physician with kanamycin. On the day before her admission, she had nausea, vomiting, and serious abdominal pain. She was treated by another physician who is specialized in gastrointestinal disease under a diagnosis of acute gastric ulcer. Despite discontinuation of sulindac, her abdominal pain continued and her rash became generalized by the following day when she was admitted to a large emergency hospital.

She had no history of severe drug reactions in the past and had no recent symptoms of an upper respiratory tract infection.

At the time of admission, she was an acutely ill woman with a fever of 38°C. There was conjunctivitis, a generalized maculoerythematous rash with scattered vesiculobullous lesions with sloughing of epidermis and a positive Nikolsky sign. There was ulceration of the buccal, the gastric, and the rectal mucosa and the external genitalia. The laboratory data were notable for the following: Hemoglobin value, 14.8 g/dl; WBC count, 2500/mm^3; platelet count, 119,000/mm^3; SGOT, 3978 IU/l (normal: 12–32 IU/l); SGPT, 2763 IU/l (6–25 IU/l); lactic dehydrogenase (LDH), 6027 IU/l (200–500 IU/l), and bilirubin, 2.4 mg/dl (0.2 to 0.9 mg/dl). Despite vigorous treatment including intensive supportive care, hemodynamic monitoring and corticosteroids, the patient died on the 3rd hospital day, 18 days after she started taking sulindac. After 12 h, she was autopsied under the suspicion of medical malpractice.

Autopsy Findings

The decedent was 156 cm tall, weighed approximately 53 kg, and showed a moderate degree of rigor mortis in her lower legs. The rectal temperature was

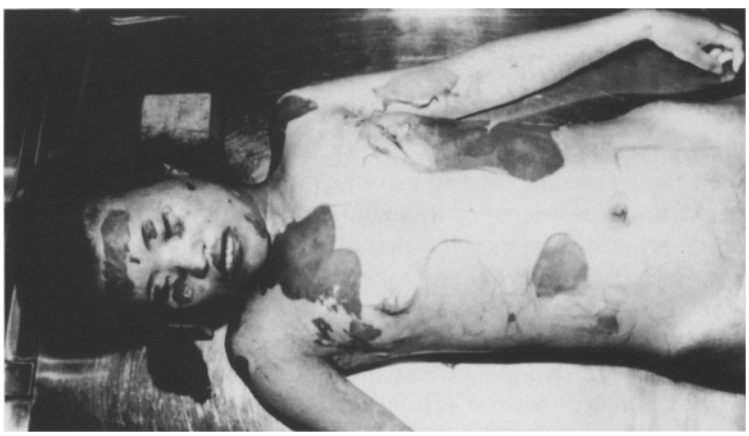

Fig. 1. Face, chest, and abdomen showing large areas of denuded epidermis

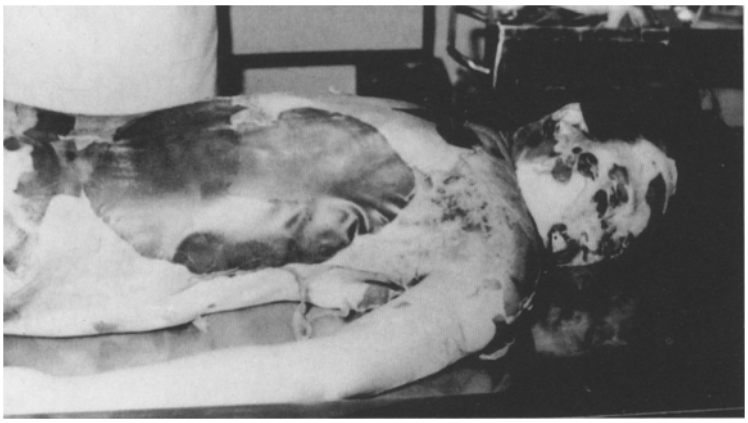

Fig. 2. Back showing extensive sloughing of epidermis

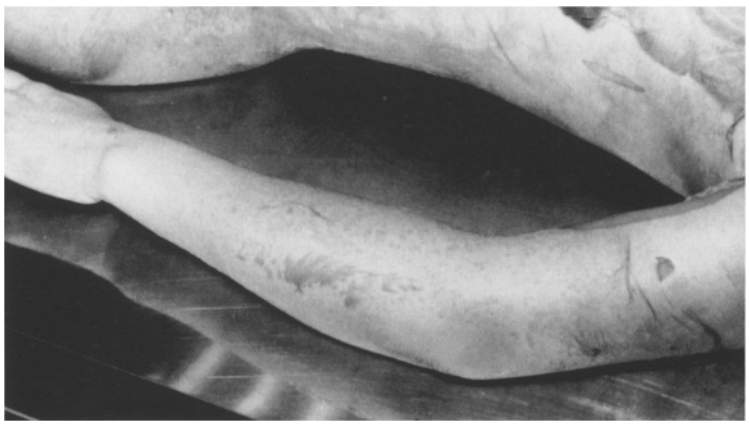

Fig. 3. Skin lesions over left arm showing flaccid vesicles

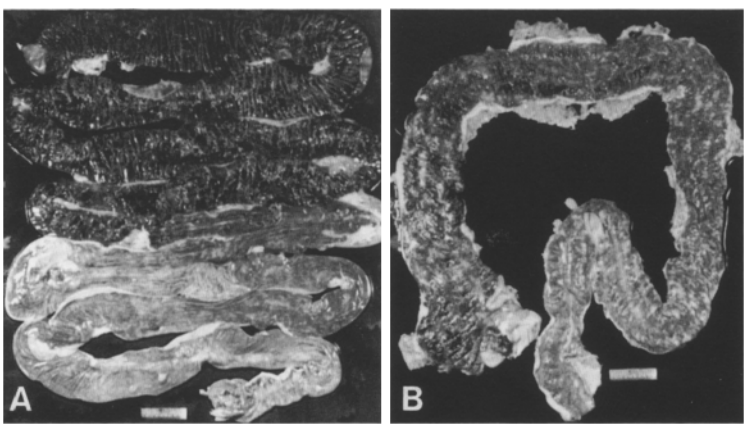

Fig. 4A, B. Mucosal erosive lesions and severe submucous hemorrhages of duodenum and jejunum (**A**), and those of colon (**B**)

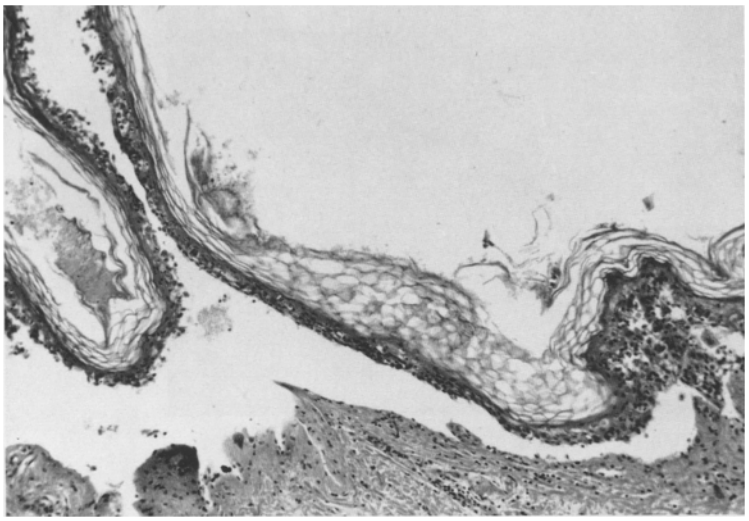

Fig. 5. Skin vesicle. Skin peel showing full-thickness epidermal separation from dermis. Inflammatory cells are present in the upper dermis. HE, × 100

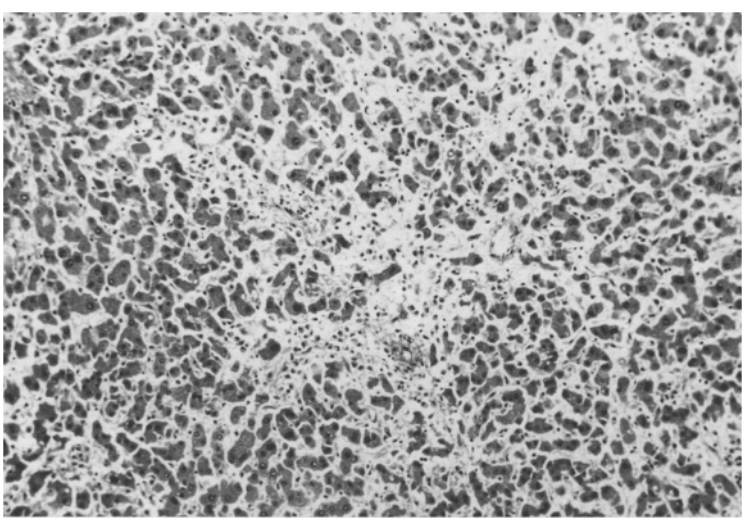

Fig. 6. Liver showing patchy central lobular necrosis and patchy cell development. HE, × 100

36°C. Large areas of skin on her face, neck, chest, abdomen, and back had been denuded of epidermis (Figs. 1, 2). The lips and the oral mucosa were also involved. There were many vesiculobullous lesions on her extremities which were flaccid and sloughed on palpation (Fig. 3). There was 200 ml of reddish fluid in the abdominal cavity. Some erosive lesions and severe submucous hemorrhages covered the mucosa of larynx, trachea, and bronchi. There was a great amount

of reddish frothy mucous in the trachea and bronchi. The liver was slightly enlarged and yellowish brown. The kidneys were of usual size and slightly anemic in the cortex on section. A patchy mucosal epithelial cell necrosis, degeneration, and severe submucous hemorrhages of the gastric body, duodenum, jejunum, and colon were disclosed (Fig. 4). The mucosa of the other parts of gastrointestinal tract was severely edematous and easily sloughed.

On microscopic examination, skin vesicles showed necrosis of the epidermis with subepidermal separation from the dermis. Inflammatory cells were present in the upper dermis (Fig. 5). Most hepatocytes were normal, but mild, patchy central lobular necrosis and patchy cell development were noted (Fig. 6). There was no evidence of infection microscopically.

Blood and bullous content cultures for bacteria showed no growth.

Discussion

The present case had the extensive sloughing of epidermis, skin vesicles, and mucosal erosive lesions during sulindac therapy. Skin vesicles showed necrosis of the epidermis with subepidermal separation from the dermis on microscopic examination. These features were typical of the Lyell syndrome. The extracellular fluid was lost from the lesions of epidermal defect and gastrointestinal mucosal lesions. The cause of death was considered to be severe metabolic acidosis, hyperkalemia, coagulopathy, and finally hypovolemic shock.

In adults, the Lyell syndrome has been generally considered to be a drug-induced disease [6], although cases of Lyell syndrome in adults that may have been of staphylococcal origin have been reported [7]. In our case, blood and bullous content cultures for bacteria showed no growth, and no infectious symptom had been seen before the onset of Lyell syndrome. The liver dysfunction was considered to be drug-induced toxic hepatitis. The microscopic findings of the skin vesicles revealed dermal/epidermal split and inflammatory cell development in the upper dermis, which were consistent with drug-induced Lyell syndrome [8]. No medication other than sulindac had been taken for at least 1 month before the onset of her eruption. From the facts, the present case was considered to be sulindac-induced Lyell syndrome that resulted in a fatal outcome.

Although the package insert for sulindac lists hypersensitivity as an adverse effect, Lyell syndrome induced by sulindac has been relatively rare and the patients had usually recovered after sulindac therapy was discontinued [2]. We have known only two published case reports of fatal Lyell syndrome induced by sulindac [4, 5]. In our case, if sulindac therapy had been discontinued when the initial slight fever and skin eruption developed, the decedent could have had any chance of recovery. Recent reports of other adverse effects with sulindac [9, 10] suggest that sulindac may have potentially more serious toxicity than has been recognized. The doctor who prescribed sulindac therapy should have used more caution in prescribing it and avoiding the fatal outcome of the patient.

After the conclusion that we proposed, the professional error was reputed malpractice.

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