Fulminating Hepatic Necrosis in a Patient with Multiple Myeloma Treated with Urethane

Report of Case

By BARBARA E. HAZLETT, H. E. TAYLOR AND D. M. WHITELAW

URETHANE (ETHYL CARBAMATE) is frequently used in the treatment of malignant disease and its toxic effect on the hemopoietic system is well known. It is less well appreciated that this drug may produce fulminating hepatic necrosis. The English literature holds reports of three such fatalities,1, 2, 3 and it seemed the most probable explanation of the case to follow.

CASE REPORT

Mrs. D. H. (No. A-53-969), a 62 year old, married, white woman was admitted to hospital in August of 1953 for investigation of low back pain which radiated into the right hip and which was of six weeks' duration. Six months prior to admission she had had cervical pain of sudden onset which radiated into her shoulders and was aggravated by movement. This pain lasted three months and then gradually receded, leaving residual paraesthesias in her hands. In these six months her weight dropped from 175 to 123 pounds. She had noticed drooping of her right eyelid for one year and a gradually enlarging lump on the back of her head for seven months, but as both were painless, she had not sought medical attention.

Physical examination revealed ptosis of the right eyelid with an associated small right pupil. There was a soft, fluctuant, non-tender swelling which measured 8 x 10 cm. in the right parieto-occipital region. Examination of the cardiovascular and respiratory systems showed them to be normal. No masses were palpated in the abdomen. There was tenderness over the fifth cervical vertebra and over the tenth ribs. All peripheral joints moved painlessly through a normal range. Hoffman's sign was present bilaterally and the plantar responses were extensor. Pain sensation was diminished in the left leg and vibration sense was absent in the right foot. A Rumpel-Leeds' test was positive.

Laboratory investigation revealed a hemoglobin of 68 per cent (9.9 Gm.) and a red blood cell count of 3,100,000 per cu. mm. The red cell morphology was fairly regular although there was marked rouleau formation. The erythrocyte sedimentation rate was 26 mm. per hour, Westergren. The white cell count was 7,350 per cu.mm. with a normal differential. The coagulation factors were normal. The sternal marrow showed 8.7 per cent plasma cells, 51 per cent proplasma cells and 1.3 per cent plasmoblasts. The serum albumin was 3 Gm. per cent and serum globulin 10.2 Gm. per cent. The liver function tests were otherwise normal. The N.P.N. was 39 mg. per cent. The serum calcium was 9.4 mg. per cent.

The urine specific gravity ranged between 1.015 and 1.022. The average protein excretion was 150 mg. per cent (4 plus). The sediment contained 1 plus white blood cells and occasional red blood cells. Bence-Jones protein was repeatedly present.

A skeletal radiological survey showed generalized demineralization of bone, with a compression fracture of the fifth cervical vertebra, such that the vertebral body was extruded posteriorly. There were several punched out areas in the ribs, humeri and skull. A soft tissue tumor containing calcium was seen eroding the right parietal and occipital bones.

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The diagnosis of multiple myeloma having been established, the patient was treated with deep X-ray therapy to the lower spine, cortisone 100 mg. daily and urethane 3 Gm. daily in divided doses.

This therapy was started in hospital and the patient obtained some relief of pain. After thirteen days of therapy, the white cell count was 4,100 per cu. mm. and the sedimentation rate 118 mm. per hour. On the thirty-ninth day the white cell count was 2,600 per cu. mm. with 78 per cent polymorphonuclear leucocytes; the platelet count was 511,000 per cu. mm.

On the forty-eighth day of treatment, the patient had generalized continuous convulsions and purpuric lesions; she died within twenty-four hours, in another hospital. Only two days prior to death she had reported that she felt "better than usual".

Autopsy findings: The autopsy was done sixteen hours after death. Petechial hemorrhages were noted on the extremities and there were ecchymoses on the eyelids and lips. The pupils were equal. There was moderate hemorrhage in the left retropleural and retroperitoneal tissues. The lungs were congested and edematous posteriorly. There was also localized edema of the right upper lobe. The liver weighed 2100 grams. The external surface, although smooth and of normal contour, was mottled red and yellow. The consistency was not unusual. The cut surface had an exaggerated nutmeg appearance. Several small areas 1 to 3 cm. in diameter were pale and apparently bloodless. The kidneys weighed 200 grams each. Apart from generalized pallor, they were normal macroscopically. The heart, gastro-intestinal system and spleen were normal on gross examination. A soft jelly-like mass bulged a distance of 3 cm. from a scalloped defect in the right parietal and occipital bones which measured 8 cm. x 10 cm. (fig. 1). The mass was adherent to the dura but not to the scalp. It had not invaded the dura or the intracranial space. It contained eggshell fragments of bone. On section, the mass was greyish-pink and gelatinous peripherally, and dark red centrally. The marrow at the lower end of the sternum was replaced by dark red and greyish jelly-like tissue. The lumbar vertebrae were examined and there was a similar gelatinous involvement of the marrow of L5 and L6. The right side of the body of L5 was obviously infiltrated by this abnormal tissue. There had been complete destruction resulting in collapse of the right side of the fifth lumbar vertebral body. The brain was normal.

Microscopic findings: The liver showed massive central hemorrhagic necrosis. The few hepatic cells remaining in the portal tract areas were markedly vacuolated. The reticulin frame work of the liver was intact (figs. 2 and 3). The left ventricle contained small areas...
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Fig. 2.—Section of liver showing a few cords of vacuolated liver cells about a portal tract—and hemorrhagic necrosis elsewhere. X125. Hematoxylin and eosin.

Fig. 3.—Section of liver showing a few viable liver cells with pyknotic nuclei remaining near a portal vein. Ghostlike remnants of necrotic liver cells and hemorrhage make up the rest of the picture. X200. Haematoxylin and eosin.

of perivascular fibrosis. These did not contain amyloid material. The lungs revealed deeply eosinophilic edema fluid which appeared more dense than the edema of heart failure. There was no evidence of a granulomatous reaction. In the kidneys were a few dense, cellular, so-called “Bence-Jones” casts. About these was minimal proliferative reaction. No giant cells were seen. The splenic pulp contained an increased number of plasma cells, some of
which were giant forms. Section of the upper end of the oesophagus showed a small area of acute mucosal necrosis devoid of inflammatory reaction. The cranial tumor contained sheets of plasma cells between areas of hemorrhage and necrosis. The sternal and vertebral marrow showed large numbers of plasma cells with marked hypoplasia of other marrow elements. Sections of submaxillary gland, ovary, adrenal, pancreas, thyroid, diaphragm, cervix, tongue, stomach, jejunum, and ileum were histologically normal.

**DISCUSSION**

Animal experimentation has suggested that urethane is a hepato-toxin. Mostofi and Larsen⁴ produced acute congestion, edema, and vacuolation of liver cells in mice, within thirty minutes of the injection of a sublethal dose of urethane. Only five minutes after a lethal dose in the rat, Doljansky and Rosin⁵ were able to find hemorrhage in the portal and central areas of the liver.

In two¹ ² of the three reported human cases of hepatic necrosis due to urethane, the indication for the use of this drug was multiple myeloma and the dose ranged from 2 to 6 Gm. per day for twelve and twenty-two months. In the third case,³ the primary disease was carcinoma of the prostate and the drug was given in larger dosage, e.g., 9 to 16 Gm. daily for forty-eight days. Meacham et al.¹ described the pathological changes in the liver as atrophy, necrosis, and vacuolation of the centrilobular cells. They remarked on the presence of subintimal edema with fragmentation and necrosis of the walls of the central veins and portal blood vessels, suggesting that the hepatic changes were secondary to a specific vascular lesion.

Our case aroused considerable clinical interest for a number of reasons. She presented a large, always painless, soft tissue myeloma of the calvarium. She had an unusually high serum globulin (i.e., 10.2 Gm. per cent). Despite the possible protective action of cortisone, she had a definite leucopenia after six weeks on moderate doses of urethane, and she died most unexpectedly of acute hepatic insufficiency after only seven weeks of treatment. In the months previous she had not received blood or blood products, nor had she had any prodromal symptoms of malaise or anorexia, making it most unlikely that she had hepatitis of viral etiology. Histologically the massive centrilobular hemorrhage and necrosis so obscured the central veins that the angionecrosis described by Meacham could not be observed. Thus urethane would seem to be the agent most probably responsible for this woman's death. The very rapid terminal phase was noteworthy in this case and in those that have been reported. In none was a history of previous allergy recorded. It is probably only coincidence that both reported cases of myeloma also had unusually high serum globulin levels, i.e. 7.9 Gm. per cent and 10.9 Gm. per cent. Rundles et al.⁶ reported two cases of myeloma who died of a less acute hepatic necrosis in the weeks following prolonged urethane therapy. Liver biopsy in one case showed central and mid-zone hepatic degeneration and fibrosis, and in the other, centrilobular hemorrhage or severe congestion and parenchymal degeneration. Death was not definitely ascribed to urethane or to any other exogenous agent by the authors, but the details are suggestive of a hepato-toxic mechanism similar to that described in this paper.

In this case there was a fall in the white blood count from 7350 per cu. mm. to 4100 per cu. mm. after thirteen days of treatment and to 2600 per cu. mm. after thirty-nine days of treatment. This might have been construed as indica-
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tive of over-dosage and the amount of drug might have been reduced to avoid irreversible bone marrow depression.

Generalized hemorrhage which she showed clinically and which was found at autopsy may have been due to thrombocytopenia but was more likely attributable to hypoprothrombinaemia due to extensive liver necrosis.

The considerable and rapid loss of weight was no doubt a contributing factor to the appearance of hepatic necrosis, since malnutrition could be expected to interfere with normal liver function, making the liver cells more vulnerable to attack by a toxic agent.

Conclusions

A case of multiple myeloma treated for forty-eight days with combined urethane and cortisone is reported.

The patient died of acute hemorrhagic centrilobular hepatic necrosis believed due to urethane. Three similar reports have appeared in the literature.

Conclusiones in Interlingua

Es reportate un caso de multiple myeloma tractate durante 48 dies con urethano in combination con cortisona.

Le patiente moriva de acute necrosis hepatic centrilobular hemorrhagic que nos considera como debite al action de urethano. Tres simile reportos se trova in le literatura.

References

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