6-Thioguanine as a cause of toxic veno-occlusive disease of the liver

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SUMMARY Lesions of hepatic veno-occlusive disease were found in the needle biopsy specimen of one patient suffering from chronic granulocytic leukaemia and in the liver at necropsy of a second patient suffering from acute myeloid leukaemia. The treatment included administration of 6-thioguanine which was the only relevant compound used in the first patient and which was combined with cytosine arabinoside in the second patient.

Occlusion of the hepatic efferent venous system is a condition which is uncommon in clinical practice although Kelsey and Comfort described a series of patients in whom the lesion was found without clinical effects. The most easily recognised form of occlusion is that involving the major hepatic veins, often in close proximity to their ostia, the recognition of this syndrome being attributed to George Budd in 1845. Such major occlusions are generally distinguishable from lesions involving small intrahepatic veins or venous radicles which are known to be affected in a variety of conditions. Probably the most widely distributed hepatic veno-occlusive disease (VOD) is that associated with plant toxins and such effects have been found in patients who had ingested pyrrolizidine alkaloids usually extracted from species belonging to Senecio, Crotalaria, Heliotropium and Cynoglossum genera. More recently, the syndrome of veno-occlusive disease has been noted in patients not exposed to such plant toxins and lesions of the small hepatic veins are now known to develop after supervoltage irradiation and after administration of certain drugs. These include azathioprine and the possibility of similar changes being induced by other therapeutic compounds has been canvassed. Urethane has been implicated and recently similar changes have been reported in two patients who died with acute myeloid leukaemia and who had been treated with cytosine arabinoside and 6-thioguanine. The authors considered that the veno-occlusive changes were associated with the combination therapy, but were not able to identify which of the two compounds was responsible for the lesions.

The present report concerns two patients suffering from leukaemia, who developed hepatic VOD while being treated with 6-thioguanine and only one of whom had also received cytosine arabinoside.

Case reports

CASE 1
A 33-year-old man was referred from Spain with a diagnosis of chronic granulocytic leukaemia. An enlarged spleen was palpable, the WBC was raised to $320 \times 10^9/l$, platelets to $315 \times 10^9/l$ and the haemoglobin was 15 g/dl. He had been treated for two weeks with busulphan 6 mg/day and allopurinol 600 mg/day. He was first seen at Hammersmith Hospital where hepatosplenomegaly was noted after a two-week course of busulphan. No treatment was given for two weeks and the patient was then subjected to leukopheresis and the cells were cryopreserved. At this time he was given 50 mg busulphan and this was followed a week later by 100 mg busulphan. Over the next four months, he received intermittent courses of 6-thioguanine at 80 or 40 mg/day at the end of which time the total dosage of 6-thioguanine was 7.64 g. Splenectomy was then carried out and a wedge biopsy specimen was taken of the liver including what the surgeon described as a 'mottled white patch.' He developed a severe intraperitoneal haemorrhage two days later for which he had a second laparotomy and melaena for which he was treated with cimetidine. He made a good recovery and appeared quite well six months after his first attendance at the hospital.
CASE 2
A 33-year-old woman was referred from Holland with a diagnosis of acute myeloid leukaemia. She had been treated (1976) four years previously for Hodgkin’s disease (stage IIa mixed cellularity) by irradiation to neck, axilla, mediastinum and lumbar regions using Telecobalt x-ray in 30 fractions with normal mantel field shielding. For six months after this treatment, vinblastine had been administered and the result was reported as complete remission.

In March 1980, acute myeloid leukaemia was diagnosed and three cycles of combination therapy administered. This included 6-thioguanine (5.04 g), cytosine arabinoside (4.2 g) and daunorubicin (0.54 g) with partial remission. Thereafter a form of maintenance therapy was given in Holland, the details of which are not available. In August 1980, the patient was prepared for bone-marrow transplant with 6-thioguanine (1.76 g), cytosine arabinoside (1.76 g), daunorubicin (0.252 g) and 800 rads total body irradiation, the transplant being performed on 13 August.

Diarrhoea developed two days later, pyrexia after six days and jaundice and distention 10 days post transplant. Although a graft versus host reaction was entertained clinically a skin rash was never observed.

The patient died on the 16th post graft day with oedema, ascites and renal failure. At limited necropsy ascitic fluid (2200 ml) was found and a liver weighing 2300 g, showing the mottled appearance associated with venous occlusion. No thrombosis was found in major hepatic veins or ostia.

LIVER LESIONS
Case 1
Sinusoids in several parts of the section surrounding hepatic venous radicles of the resected wedge of liver tissue were crowded with erythrocytes, the intervening hepatic plates being compressed and rich in lipofuscin pigment (Fig. 1). Much hepatocyte hyperplasia was noted in remaining parenchyma, particularly in periporal regions of the liver in which vascular relations appeared to be retained (Fig. 1). Some of the hepatic venous radicles showed intimal hyperplasia which in parts included excessive...
collagen (Figs. 2 and 3). Foci of extramedullary haemopoiesis were present.

Case 2
Macroscopically foci of congestion involving irregular regions throughout the liver were separated by pale hyperplastic regions in which large lobules could be identified. Large hepatic veins, hepatic vein ostia and inferior vena cava did not contain thrombi (Fig. 4). There was evidence of much erythrocyte accumulation in sinusoids with destruction of hepatocyte plates and sinusoidal distention (Fig. 5). The sublobular hepatic veins and hepatic venous radicles showed marked intimal fibrosis and
oedema with striking reduction of lumina (Fig. 6 and 7). In some parts of the venous wall erythrocytes had accumulated. The features represented VOD.

Discussion

So far as the first patient is concerned, the intrasinusoidal crowding of erythrocytes together with venous radicular changes indicate VOD. A major ostial occlusion seems unlikely because of the scattering and separation of the lesions with intervening normal parenchyma. Of the possible causes for these changes, it is certain that no irradiation was administered and the patient had never, so far as he was aware, taken pyrrolizidine alkaloids or other unusual form of plant extract. Of the compounds he received, busulphan was given on only three occasions and the last dose was administered four months before the biopsy section was taken. In any case busulphan is reported as inducing cholestatic jaundice only. Allopurinol sometimes associated with a mild hepatitis and granulomas but not VOD was given for a short period, four months before the biopsy was taken. The main therapy was 6-thioguanine. The second patient showed clear evidence of VOD lesions in the veins and was also treated with 6-thioguanine. Cytosine arabinoside and other chemotherapeutic agents had been administered about the time of her transplant and these cannot be excluded as contributory factors. The whole body irradiation is unlikely to have played any part as the level of hepatic irradiation usually reported with VOD changes is generally about 3000 rads. Although our first patient appears to be the first who has developed these changes after receiving 6-thioguanine without cytosine arabinoside, several patients have developed signs of hepatotoxicity with veno-occlusive changes while being treated with 6-thioguanine and cytosine arabinoside as occurred in our second patient. Thus the patient of Jacobs et al could well have suffered veno-occlusive disease as a result of 6-thioguanine although the therapy included whole body irradiation as well as cytosine arabinoside. The dosage of irradiation (1000 rads) is lower than that usually associated with irradiation veno-occlusive hepatic changes and the lesion is likely to be a result of drug toxicity. The two patients of Griner et al also clearly showed signs of VOD and the main chemotherapy included 6-thioguanine and cytosine arabinoside although one had some exposure to cyclophosphamide. The morphological changes were similar in the liver sections taken at necropsy from the above mentioned three patients. The letter of Penta and his colleagues includes reports on liver biopsy sections of five patients who had sinusoidal congestion “without changes in caliber of the central veins.” The authors do not stipulate the therapy particular patients received but it appears from their Table that some may have had 6-thioguanine, either alone or combined with other therapy. VOD has been described also in patients showing the lesions of graft versus host disease after bone marrow transplantation. All the patients with this lesion had been treated with radiotherapy and chemotherapy. Both patients described by Sloane and his colleagues had been given a variety of chemical compounds including 6-thioguanine and of the three patients who had not received radiotherapy in the series by Berk et al two had been given 6-thioguanine together with other compounds and one was reported as receiving only cyclophosphamide. This compound had not been given to one of the patients reported here. Although our first patient has not been investigated by anatomical dissection of the veins, the microscopical findings are sufficient to make a clear diagnosis of VOD. In our second patient, the ostia were clear.
Fig. 6 Conspicuous oedematous and fibrous occlusion of sublobular vein with intramural erythrocytes. Haematoxylin and eosin ×400

Fig. 7 Reticulin silver impregnation of same lesion as shown in Fig. 6. Gordon and Sweet ×400
The diagnosis in our first patient is probably the first biopsy report of VOD associated only with 6-thioguanine toxicity and the survival of the patient after the biopsy has permitted a follow-up of the patient’s course. It seems that the lesion is not progressive provided the therapy is discontinued. The question of the fatal outcome in our second patient may be related possibly to an increased concentration of 6-thioguanine in the liver which could result from simultaneous absorption of cytosine arabinoside, a phenomenon known in animal experimental work. In respect of the dosage used, it is interesting that our first patient survived with a dose of 7·64 g of 6-thioguanine without cytosine arabinoside and three others, all adults, in which we have been able to calculate dosage (two of Griner et al and our second patient) had lower doses of 6-thioguanine (7·0, 6·9, and 6·8 g).

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References

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