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*Case report*

# Peliosis hepatis induced by 6-thioguanine administration

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SUMMARY **A patient with acute myeloblastic leukaemia developed jaundice revealing peliosis hepatis after receiving 6-thioguanine for two months. Peliosis hepatis was severe and was associated with mild lesions of centrilobular veins. Withdrawal of 6-thioguanine was followed by a progressive improvement of liver dysfunction. This report shows that 6-thioguanine, a thiopurine already reported to be responsible for veno-occlusive disease of the liver, can induce peliosis hepatis. This suggests that some liver vascular disorders caused by thiopurines (6-thioguanine, azathioprine and 6-mercaptopurine), particularly peliosis hepatis, veno-occlusive disease, sinusoidal dilatation and perisinusoidal fibrosis, might be related syndromes caused by similar lesions at different sites.**

Peliosis hepatis is a liver lesion characterised by blood filled cavities bordered by hepatocytes, randomly distributed throughout the hepatic parenchyma.[1-7] This lesion has been described in association with various diseases including tuberculosis and haematologic disorders,[1-4] and after the administration of various drugs,[4] particularly androgens[5 6] and azathioprine, a thiopurine derivative.[7] We report the case of a patient with acute leukaemia who developed peliosis hepatis after receiving 6-thioguanine, another thiopurine derivative closely related to azathioprine and previously reported as a cause of veno occlusive disease of the liver.[8-12]

This report broadens the spectrum of liver vascular disorders caused by 6-thioguanine and suggests that péliosis hepatis, veno occlusive disease, sinusoidal dilatation and perisinusoidal fibrosis may be related syndromes resulting from a similar mechanism affecting endothelial cells at different sites.[7 13] We suggest that the initial step of liver vascular lesions caused by thiopurine derivatives might result from potentially toxic metabolites common to these drugs, whose formation rate is genetically determined.

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## Case report

A 63 year old woman was admitted for asthenia and leucopenia on 28 March 1985. Clinical examination was normal. Blood cell counts were as follows: leucocytes, 2100/mm$^3$ with 15% neutrophils, 61% lymphocytes, 13% monocytes; platelets, 182 000/mm$^3$; red blood cells, 2 820 000/mm$^3$. Bone marrow examination showed decreased normal haematopoietic precursors and numerous haemoblasts (40%). Liver tests were normal. The diagnosis was acute myeloblastic leukaemia and the patient was given cytosine arabinoside, 160 mg/day, and adriamycine, 70 mg/day, from 4 to 9 April. The subsequent bone marrow aplasia was complicated by septicemia caused by *Candida zeylanoïdes* and *Bacteroïdes fragilis* and by severe anorexia requiring total parenteral nutrition. These complications and treatment were associated with a transiently increased alkaline phosphatase activity, 300 IU (normal, 25–130 IU) and serum gammaglutamyltransferase activity, 156 IU (normal, 10–40 IU).

In May, complete remission was obtained. Recovery from infection and discontinuation of parenteral nutrition were followed by a marked decrease in serum alkaline phosphatase activity, 160 IU, and in serum gammaglutamyltransferase

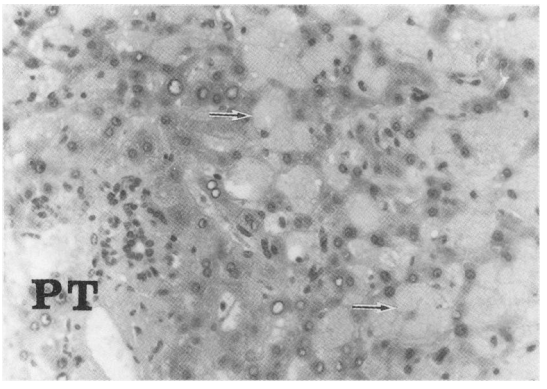


Fig. 1 *Lesion of peliosis hepatis characterised by blood filled cavities bordered by the hepatocyte plates (arrows). Haematoxylin and eosin stain.*

activity, 90 IU. The patient was discharged on 20 May, with as treatment: oral 6-thioguanine, 40 mg/day, four days/week, and intramuscular cytosine arabinoside, 100 mg/week. In July, two months later, the patient was readmitted for jaundice and pruritus. Despite these symptoms, she was in good condition. Clinical examination was normal except for jaundice and moderate hepatomegaly. There was no manifestation suggestive of portal hypertension or liver failure. Peripheral blood cell counts and bone marrow examination showed no recurrence of leukaemia. Serum conjugated bilirubin was 95 μmol/l; serum alkaline phosphatase, 335 IU; serum gammaglutamyltransferase, 131 IU; serum alanine aminotransferase, 142 IU (normal, 10–40 IU); serum aspartate aminotransferase, 274 IU (normal, 10–40 IU); prothrombin time, normal. Serologic tests for a recent infection caused by hepatitis A virus, hepatitis B virus or cytomegalovirus were negative. At ultrasonography, the liver was slightly enlarged and homogenous, and the biliary tract was normal. There was no ascites. A percutaneous liver biopsy was done and the liver sample was noted to be purplish. Histologic examination showed marked sinusoidal dilatations and blood filled cavities without endothelial lining, randomly distributed throughout the liver lobules (Fig. 1). There were only mild lesions of some centrilobular veins consisting in eccentric thickening of venous walls without obstruction of the lumen. There was no cholestatis, no hepatocyte necrosis, nor infiltration by leukaemic cells.

On 23 July 1985, cytosine arabinoside and 6-thioguanine administration was discontinued. In October, three months later, jaundice had markedly decreased and serum conjugated bilirubin was 25 μmol/l. Blood cell counts, however, showed the recurrence of leukaemia. Cytosine arabinoside was readministered alone from 25 November to 17 December 1985, and in association with mitoguazone in January 1986, and with daunorubicin in February 1986. These treatments did not affect the slow decrease of liver tests abnormalities, but were poorly efficient on haematologic disorders. The patient died from infection on 12 February. Autopsy was not done.

## Discussion

Peliosis hepatis revealed by jaundice in this patient can be reasonably ascribed to 6-thioguanine for several reasons. (a) There was no past history of liver disease and liver tests were normal on the first admission. (b) The transient abnormalities of liver tests observed before 6-thioguanine administration were closely related to bacterial septicaemia and total parenteral nutrition. Treatment of infection and return to oral nutrition were quickly followed by improvement of liver tests. (c) There was no serologic evidence for a recent infection caused by hepatitis A virus, hepatitis B virus or cytomegalovirus. (d) The role of haematologic disorders is unlikely: leukaemia was in remission when peliosis hepatis developed and liver function improved despite recurrence of leukaemia. (e) Jaundice revealing peliosis hepatis occurred two months after the onset of 6-thioguanine and cytosine arabinoside administration, the only two drugs given during this period. Jaundice and abnormalities of liver tests decreased after 6-thioguanine withdrawal. The direct role of cytosine arabinoside is unlikely because its repeated readministrations did not interfere with the improvement of liver function. The contribution of this drug to 6-thioguanine toxicity cannot be excluded, however.

The clinical manifestations associated with peliosis hepatis include hepatomegaly,[5–7] liver failure,[2] portal hypertension,[7] and intraperitoneal bleeding.[6] In our patient, peliosis hepatis was revealed by marked cholestasis without liver failure or portal hypertension. Such a presentation has been seen in few patients with peliosis hepatis due to azathioprine (Degott, personal data). The possibility that peliosis hepatis was not responsible for jaundice, however, but only an associated asymptomatic lesion caused by the same drug, cannot be excluded. Indeed, thiopurine derivatives can induce cholestasis without peliosis hepatis[14–16] and, in the absence of histologic follow up, it is not known whether peliosis hepatis lesions decreased as cholestasis disappeared in our patient.

6-Thioguanine has been reported to induce veno-occlusive disease.[8–12] The case of our patient with peliosis hepatis broadens the spectrum of liver

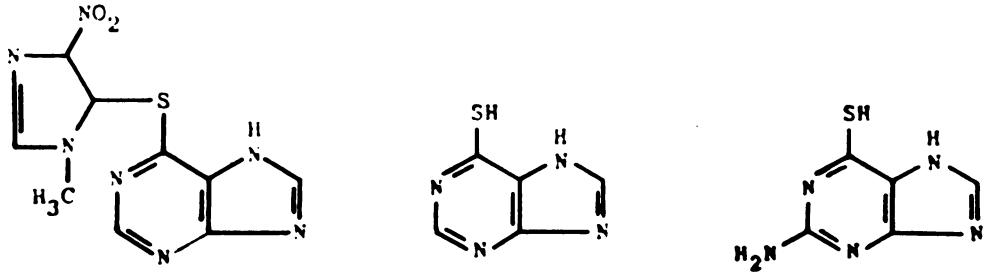


Fig. 2 *Chemical structure of 6-thioguanine, azathioprine and 6-mercaptopurine.*

vascular disorders caused by this drug. It is noteworthy that azathioprine and its derivative 6-mercaptopurine, two other thiopurines with chemical structures closely related to that of 6-thioguanine (Fig. 2), can induce similarly liver vascular disorders. Indeed, azathioprine has been involved in peliosis hepatis,[7] veno-occlusive disease,[13 17 18] sinusoidal dilatation,[19] and perisinusoidal fibrosis[20 21] whereas 6-mercaptopurine has been responsible for veno-occlusive disease[22] and perisinusoidal fibrosis.[20] These observations suggest that these diseases may represent different syndromes resulting from a similar initial lesion involving endothelial cells at different sites, sinusoidal walls for peliosis hepatis, sinusoidal dilatation and perisinusoidal fibrosis, and centrilobular veins for veno-occlusive disease. This view is reinforced by the following observations: (1) mild lesions of centrilobular veins were associated with peliosis hepatis, the prominent lesion, in our case and in another report;[7] similarly, marked veno-occlusive disease was associated with peliosis hepatis in other patients;[13] (2) electron microscopic findings have shown marked sinusoidal endothelial damage consisting in increased endothelial permeability and passage of red blood cells into the space of Disse, in veno-occlusive disease and peliosis hepatis.[4 23 24]

The mechanisms by which 6-thioguanine, azathioprine and 6-mercaptopurine induce vascular lesions of the liver are unknown. The role of toxic metabolites common to these drugs, however, might be suggested. Indeed, these three thiopurines have several metabolic pathways in common, particularly, the transformation into 6-thioguanine nucleotides by hypoxanthine guanine phosphoribosyltransferase and S-methylation by thiopurine methyltransferase (TPMT) (Fig. 3).[25 26] The cytotoxic activity of 6-mercaptopurine is partly caused by the incorporation

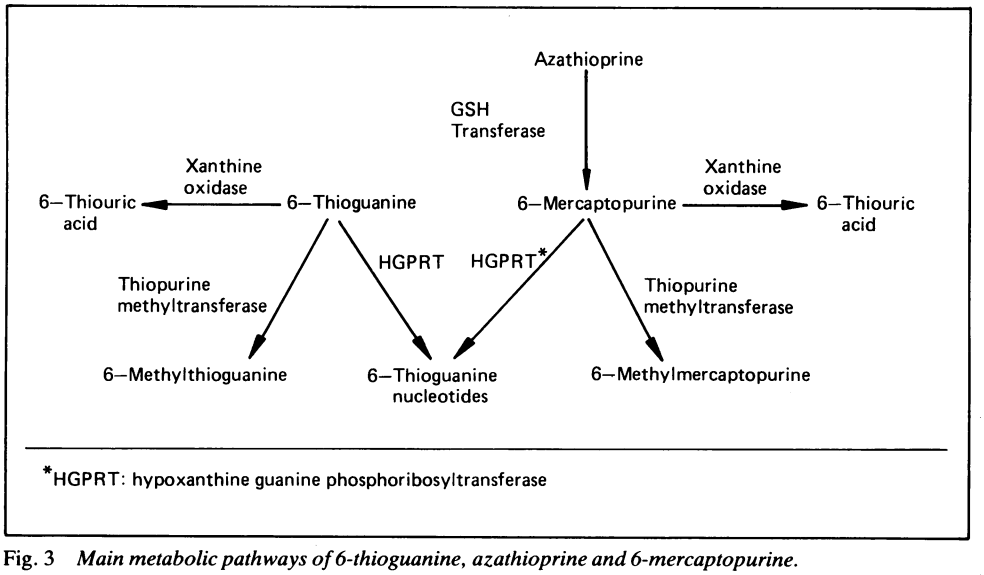


Fig. 3 *Main metabolic pathways of 6-thioguanine, azathioprine and 6-mercaptopurine.*

into DNA of 6-thioguanine nucleotides.[27] Moreover, the risk of developing some adverse reactions with these drugs – bone marrow depression, megaloblastic anemia, actinic keratoses and malignant skin tumour – is related to a high formation rate of red blood cell 6-thioguanine nucleotides,[28-32] probably secondary to an impairment in S-methylation capacity because of the genetic deficiency in TPMT activity.[33] The deficiency in red blood cell TPMT activity is complete in 0·3% of subjects and partial in 11% of subjects.[33] This deficiency is similarly present in other tissues or cells containing TPMT activity such as kidney[34] or lymphocytes.[35]

From these data, it would be tempting to speculate that peliosis hepatis, sinusoidal dilatation, perisinusoidal fibrosis, and veno-occlusive disease caused by thiopurines, might result from the aggression of endothelial cells of sinusoids or centrilobular veins, by toxic 6-thioguanine nucleotides formed *in situ* or delivered from red blood cells. The risk of developing such toxic reaction may be particularly high in subjects with a high formation rate of 6-thioguanine nucleotides resulting from the genetic deficiency in thiopurine methyltransferase activity. In addition, the concomittent administration of cytosine arabinosine may have further increased the toxicity of 6-thioguanine. Indeed, the combination of both drugs in animals results in increased concentration of 6-thioguanine in the liver.[36]

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