Thorotrast administration followed by myelofibrosis

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Summary
A case of myelofibrosis related to thorotrast administration is described. Current concepts of acute myelofibrosis are discussed, as are the varied complications of thorotrast.

Introduction
Thorotrast (thorium dioxide) was introduced in 1930 as a diagnostic test for visualization of the liver and spleen, renal pelvis, body cavities and for angiography. Following widespread usage it began to be discontinued in 1947 as complications arising from its use developed. A case is now reported of myelofibrosis in a patient who had received thorotrast 29 years previously.

Case history
A 73-year-old lady presented in December of 1975 with a 6-week history of malaise and dyspnoea on exertion. In 1947 she had undergone an operation to remove cervical sympathetic ganglia because of Raynaud’s phenomenon. There was no other past medical history of significance.

On examination she appeared anaemic, with signs of mild congestive cardiac failure. There was no lymphadenopathy or hepatosplenomegaly.

A blood count showed a pancytopenia: red cell count 1.22 x 10^6/l, Hb 4 g/dl, WCC 2.4 x 10^9/l (20% neutrophils, 79% lymphocytes, 1% myelocytes), platelets 55 x 10^9/l. The peripheral blood film showed anisocytosis and occasional target cells. Careful scrutiny revealed a few tear-shaped poikilocytes, nucleated red blood cells, myelocytes and Howell-Jolly bodies. A few blast cells were also seen. Routine biochemistry was normal, as were vitamin B12, folate and serum iron levels. Plasma urate and leucocyte alkaline phosphatase score were also normal.

Sternal marrow punctures twice resulted in a dry tap. An iliac crest trephine biopsy was performed and showed decreased fat spaces and fibrosis. Silver stains showed abundant reticulin fibres, the picture was that of myelofibrosis (Fig. 1). A plain X-ray of the abdomen suggested previous thorotrast administration, with a characteristically shrunken spleen and abdominal lymph nodes which appeared to be calcified (Fig. 2). Using a gamma scintillation counter, radioactive emission was recorded over the surface of the spleen, liver and thigh. The results were 1777, 3512 and 3622 counts/100 s respectively, compared with a background count of 20/100 s.

Retrospective analysis of old case notes revealed that the patient had received an injection of thorotrast into her brachial artery immediately before her operation in 1947. This had been given to demonstrate the arterial circulation.

Despite normal folate levels, and the absence of megaloblasts, prophyllactic folate was prescribed. The patient survived for 8 months after the initial presentation, although she required increasingly frequent blood transfusions and developed several minor infections. She was then admitted in a collapsed state, with Gram-negative septicaemia, and died. A peripheral blood film during her final illness showed 26% blast cells but was otherwise similar to previous films.

Gross post-mortem examination, 19 hr after death, revealed a heart of normal size, with a vegetation on the posterior cusp of the mitral valve. The liver was enlarged and contained scattered abscesses, whilst the spleen was small and firm. Red marrow extended to the centres of the long bones.

On microscopic examination the mitral valve showed non-bacterial thrombotic endocarditis. Thorotrast was found lying free within the connective tissue stroma of the liver (Fig. 3). The iron stores were increased and there was evidence of extra-medullary haemopoiesis, with numerous megakaryocytes. The spleen showed loss of the normal follicular architecture, with deposits of thorotrast in the stroma, and haemosiderin pigment in the histiocytes.

Sections of bone marrow from the sternum, iliac crest and vertebrae showed a hyperplastic marrow. The cells had a uniform, immature appearance, and normal fat spaces were not seen. Numerous haemosiderin-laden phagocytes were present, and iron stores were increased. Reticulin-stained sections...
showed a complete network of branched fibres of increased density. When viewed by polarized light, refractile fibres of wavy type were seen, but this change was patchy, and less marked than that seen in the previous trephine examination.

Bacteriological studies confirmed an *Escherichia coli* septicaemia. Organs were submitted to the North Western Forensic Science Laboratory, for thorium analysis, with the following results: lung 35 parts/10⁶, liver 237 parts/10⁶, kidney 7 parts/10⁶ and spleen 5768 parts/10⁶.

**Discussion**

Thorium is a radioactive substance with a half-life of $1.4 \times 10^{10}$ years. It emits predominantly $\alpha$ radiation, which is of short penetration, and small amounts of $\beta$ and $\gamma$ radiation. The peak emission of $\alpha$ radiation can occur up to 25 years after administration because the thorium decays to form other radioactive substances which are themselves strong $\alpha$ emitters (Prezyna, Ayres and Mulry, 1953). Following administration, thorotrast is rapidly concentrated in the liver, spleen and bone marrow, where it remains.

A survey of 1100 patients who had received thorotrast showed a high incidence of complications which included granulomata and malignancies at the site of thorotrast administration, hepatic fibrosis, hepatic neoplasms and blood dyscrasias (Horta et al., 1965). The haematological complications can occur after a long latent period, and range from abnormal red blood cell morphology (Langlands et al., 1966).
extramedullary haemopoiesis is
exact
the
Williamson,
and
chronic
number
of blasts
(Anderson, Hoshino and Yamamoto,
1964), and 7 cases have been described following
thorotrast administration (Johnson et al., 1977).

Acute or malignant myelofibrosis was first
described in 1963 (Lewis and Szur, 1963) and is basically
an accelerated version of the classical variety. Particular features emphasized are the absence of
splenomegaly, pancytopenia and a rapidly downhill
course. The condition is thought to differ from
acute leukaemia because of the reticulin proliferation
in the marrow and relative absence of blast cells,
although small numbers are seen in the peripheral
blood film. There is debate as to whether acute
myelofibrosis is a separate entity since a certain
amount of marrow fibrosis can be seen in acute
leukaemia (Sanerkin, 1964). The fibroblastic response
in acute myelofibrosis appears to be a secondary
reactive phenomenon, rather than part of a neoplastic
process (Van Slyck, Weiss and Dully, 1970). However,
an increase in marrow reticulin remains an
important index of myelofibrosis, whilst a large
proportion of marrow blast cells is necessary for the
definite diagnosis of acute leukaemia (Beard and
Hamilton Fairley, 1974). Since cases of advanced
chronic myelofibrosis often have a considerable
number of blasts in the peripheral blood, and since
the exact significance of histological evidence of
extra-medullary haemopoiesis is uncertain (Modan,
1975), it is difficult to judge whether these cases of
acute myelofibrosis are really acute leukaemias.

Despite this difficulty in nomenclature such acute
cases undoubtedly occur, with several recent case
reports in the literature (Lubin, Rozen and Rywlin,
1976; Libnoch et al., 1977). There has been one case
report of the apparent co Existence of acute myelo-
fibrosis and acute myeloid leukaemia (Patel, Shah
and Rhee, 1976).

The case which has now been described resembles
the picture of acute myelofibrosis, with a rapidly
downhill course over a period of only 8 months.
Since thorotrast was isolated from the bone marrow
at post-mortem it was undoubtedly of aetiological
significance. The absence of splenomegaly in this
patient was due to splenic atrophy following thoro-
trast administration. Diminished haematopoietic
reserve might have been responsible for the rapid
course of this patient’s illness, since damage to her
reticuloendothelial system might have limited
examedullary haemopoiesis (Johnson et al. 1977).
The findings suggest a terminal blastic phase to the
patient’s illness, and the probable transition to an
acute leukaemia. Similar marrow changes at post-
mortem have been seen in recent cases of acute
myelofibrosis, with hypercellularity and infiltration
with blast cells (Lubin et al., 1976; Libnoch et al.,
1977).

The present patient presented 29 years following
thorotrast administration. Other haematological
sequelae have been recorded in patients up to 37 years
following administration (Johnson et al., 1977); similar
patients may therefore continue to be seen.

Fig. 3. Liver HE, × 280. Clumps of thorotrast lying in the stromal connective tissue.
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