Transient abnormal myelopoiesis accompanied by hepatic fibrosis in two infants with Down syndrome

N Yagihashi, K Watanabe, S Yagihashi

Abstract
Two necropsy cases of Down syndrome are reported. These showed transient abnormal myelopoiesis accompanying characteristic hepatic sinusoidal fibrosis. Numerous megakaryocytes were found in the liver of one case, but not in the other. Only eight cases of Down syndrome with simultaneous occurrence of hepatic fibrosis and transient abnormal myelopoiesis have been reported. The cases described here showed slight fibrotic changes in the hyperplastic bone marrow, which were not found in the previously reported cases of transient abnormal myelopoiesis.

Keywords: Transient abnormal myelopoiesis, Down syndrome, hepatic fibrosis, myelofibrosis.

Infants with Down syndrome often have acute but spontaneously regressing leukaemoid haematological changes, referred to as transient abnormal myelopoiesis, transient myeloproliferative disorder, or congenital leukaemoid reaction. A serious but very rarely reported complication is hepatic fibrosis. In previous necropsy studies, an increase in reticulin fibres in the bone marrow has not been described. We recently encountered two infants with Down syndrome and transient abnormal myelopoiesis accompanied by hepatic fibrosis. In addition there was a mild but distinct increase in reticulin in the hyperplastic bone marrow, unaccompanied by any increase in megakaryocytes. The necropsy findings in these patients are described and possible mechanisms for visceral fibrosis are discussed.

Case report
Case 1
Clinical course
A 2470 g female infant with Down syndrome facies and hepatosplenomegaly was delivered by caesarean section because of fetal asphyxia at 38 weeks gestation. Peripheral blood examination at birth showed an increased white blood cell count (128 800/μl) with 50% blasts. Other laboratory data showed high levels of lactate dehydrogenase (7455 U/l) and slight liver dysfunction (aspartate aminotransferase 75U/l, alanine aminotransferase 106U/l).

Following conservative treatment with blood transfusion, total parenteral nutrition, diuretics, and antibiotics, the peripheral white blood cell count was decreased (12 000–26 000/μl) and blasts disappeared without antileukaemia treatment. The total bilirubin was 68.4 μmol/l on day 20, and thereafter jaundice became severe (total bilirubin 657 μmol/l, direct bilirubin 421 μmol/l on day 48). Serum aspartate and alanine aminotransferases were within the normal range from day 5 to day 20. The infant died of respiratory and liver failure on day 53. There was no evidence of viral or syphilitic infection.

Necropsy findings
The liver showed diffuse intralobular and in-

(A) Sinusoidal fibrosis surrounding small groups of hepatocytes and cholestasis (case 1, haematoxylin and eosin). (B) Immunostaining for α-smooth muscle actin (case 1, streptavidin-biotin complex method). (C) Mild reticulin fibrosis of the bone marrow (case 1, silver impregnation). (D) Scattered atypical megakaryocytes in the fibrotic liver (case 2, haematoxylin and eosin).
terolobular fibrosis with no specific zonal distribution. The lobular hepatic architecture was not disturbed (figure, panel A). Elongated spindle cells with plump nuclei and collagen fibres were arranged along the hepatic sinusoids. These cells were immunopositive for $\alpha$-smooth muscle actin (figure, panel B; Dako) using the streptavidin-biotin complex technique. Intracellular and intracanalicular cholestasis was conspicuous and there were scattered foci of necrotic hepatocytes. Small numbers of mainly myeloid haematopoietic cells were located in the portal areas, but only very scanty megakaryocytes were found.

The bone marrow was hyperplastic, with increased numbers of myeloid cells in the main, some of which were immature in appearance. Megakaryocytes were decreased in number and normal in appearance, and there were no accumulations of blast cells. A slight diffuse increase in reticulin fibres was observed but showed no relationship to megakaryocytes (figure, panel C).

Extramedullary haematopoiesis consisting of all three haematopoietic cell lines was also found in the spleen, in which there was lymphoid depletion but no fibrosis. The pancreas showed mild perilobular and periacinar fibrosis but extramedullary haematopoiesis was not apparent. Both lungs showed bronchopneumonic changes in the upper lobes and massive haemorrhage in the lower lobes.

### Case 2

**Clinical course**

A 2434 g girl, born at 38 weeks gestation, was observed to have a mongoloid facial appearance and marked hepatosplenomegaly. Down syndrome was confirmed by demonstration of trisomy 21 (47,XX, +21). Peripheral blood examination at birth showed a high white blood cell count (89 000/\(\mu\)l) with 27% blasts, and an increased platelet count (670 000/\(\mu\)l). Bone marrow aspiration showed 17.5% blasts. Laboratory data showed increased lactate dehydrogenase (22 924 U/L), aspartate aminotransferase (1135 U/L), alanine aminotransferase (466 U/L), and total bilirubin (174 $\mu$mol/l). Following treatment with blood transfusion, diuretics, and antibiotics, the white blood cell count returned to normal and blasts disappeared on day 11. However, high values of lactate dehydrogenase (3687 U/L), aspartate aminotransferase (1079 U/L), alanine aminotransferase (223 U/L) and total bilirubin (159 $\mu$mol/l) still continued on day 22. The patient died of gastrointestinal bleeding on day 23. There was no evidence of viral or syphilitic infection.

### Necropsy findings

The liver showed diffuse sinusoidal and severe centrilobular fibrosis, but no evidence of cirrhosis. Small and large foci of necrotic hepatocytes were found in centrilobular areas. Intracellular cholestasis, fatty change, and tubular arrangements of hepatocytes were also observed. There was diffuse extramedullary haematopoiesis consisting of immature and mature myeloid cells and large numbers of atypical megakaryocytes (figure, panel D).

The bone marrow was hyperplastic with increased numbers of erythroid and myeloid series. Reticulin fibres were increased along bony trabeculae. Megakaryocytes were less marked and some were atypical, with large nonlobulated or multi lobulated nuclei. No accumulation of blast cells was found. The spleen was congested and showed focal extramedullary haematopoiesis but no fibrotic changes. The pancreas showed mild interlobular and intralobular fibrosis accompanied by a few megakaryocytes.

### Discussion

Hepatic fibrosis associated with Down syndrome and transient abnormal myelopoiesis has been reported previously (table). It is characterised by diffuse intralobular sinusoidal fibrosis and extramedullary haematopoiesis, in which megakaryocytes are prominent as in our case 2.1 Although the pathogenesis of the hepatic fibrosis remains unclear, it has been suggested that cytokines produced by infiltrating megakaryocytes may play an important role.14 Similar hepatic sinusoidal fibrosis occurs in agnogenic myeloid metaplasia. However, in one of our patients (case 1) there were few megakaryocytes in the fibrotic liver. This could be because megakaryocytes associated with the development of fibrosis might have virtually disappeared from the liver by the time death occurred. Alternatively, factors other than the megakaryocytes might have been involved. One possible factor in the genesis of hepatic fibrosis is the treatment with total parenteral nutrition.

### Table

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age at death</th>
<th>Liver</th>
<th>Bone marrow</th>
<th>Pancreatic fibrosis</th>
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<tr>
<td>Miller2</td>
<td>F</td>
<td>5 weeks</td>
<td>+</td>
<td>nd</td>
<td>=</td>
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<tr>
<td>Nakagawa3</td>
<td>F</td>
<td>77 days</td>
<td>+</td>
<td>nd</td>
<td>-</td>
</tr>
<tr>
<td>Becroft4</td>
<td>F</td>
<td>28 days</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miyauchi</td>
<td>F</td>
<td>0 days</td>
<td>+</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Present cases</td>
<td>F</td>
<td>3 days</td>
<td>+</td>
<td>=</td>
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</tbody>
</table>

F = female; M = male; MGK = megakaryocytic cells; + = many; + = few; = decreased number; = normal number; nd = not described.
in this case. It is well known that histo-
pathological changes in the liver damage of
infants and children given total parenteral nu-
trition range from mild cholestasis to fibrosis
or cirrhosis.6 Cholestasis may produce ac-
tivation of Kupffer cells, stimulating prolif-
eration and fibrogenesis of lipocytes which
then show the structural characteristics of myo-
fibroblasts,7 as found in our patients.

Proliferating blasts in transient abnormal myelo-
opoesis are known often to express antigens
characteristic of megakaryocytes.8 Acute mega-
karyoblastic leukaemia (AMKL) is often ac-
companied by myelofibrosis with a marked in-
crease in reticulin fibres. Although mech-
anisms of myelofibrosis are yet to be de-
determined in AMKL, cytotkines such as
transforming growth factor β,9 as well as platelet
derived growth factor,10 secreted from mega-
karyocytes can promote fibrogenesis. Both in-
fants described here showed slight increases
in reticulin fibre, a feature not described in
previous reports of infants with Down syn-
drome, transient abnormal myelopoiesis, and
hepatic fibrosis.1 This change might reflect an
excessive release of cytokines or growth factors
from proliferating haematopoietic cells, but not
necessarily from megakaryocytes, since these
were not increased.

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Acute hepatic and renal failure caused by
Pneumocystis carinii in patients with AIDS

R Boldorini, S Guzzetti, L Meroni, T Quirino, S Cristina, G Monga

Abstract
Clinical and pathological findings are de-
scribed in two AIDS patients with Pneu-
moctysis carinii infection who received
prophylactic treatment with nebulised
pentamidine and developed unusual
hepatic and renal failure. Histological
examination showed clumps of P carinii
massively obstructing hepatic sinuses and
portal vessels in the first patient, and
merular and intertubular capillaries in
the second. These findings could explain
the unusual clinical features, characterised by
acute hepatic and renal failure.
(J Clin Pathol 1995;48:975-978)

Keywords: AIDS, Pneumocystis carinii, hepatic failure,
renal failure.

Disseminated pneumocystosis in patients with
acquired immunodeficiency syndrome (AIDS)
is reported with increasing frequency,1 but it
appears still to be rare despite the high
frequency of Pneumocystis carinii pneumonia.2 Ex-
trapulmonary localisation of pneumocystosis has
been reported in necropsy series and in single
case reports, with the involvement of spleen,
lymph nodes, bone marrow, liver, thyroid, gut,
adrenal gland, skin, and brain.3

Extrapulmonary pneumocystosis can give
rise to unusual clinical presentation, including
thyroiditis, otitis media with mastoiditis, cut-
aneous lesions, “acute abdomen”, hepatitis
and chorioiditis, and lymph node enlargement.4
To our knowledge, there are no well docu-
cmented reports of renal failure due to P carinii.
Only a few cases of hepatic failure have been
described on the basis of the clinical findings,5
but without morphological evidence of the
type and severity of liver damage.

We describe the clinical and pathological
features of two cases of disseminated pneu-
moctysis in AIDS patients who were given
prophylactic treatment with nebulised pen-
tamidine and developed hepatic and renal fail-
ure because of severe liver and kidney damage.

Methods
Necropsy examinations were performed 12
hours (patient 1) and 17 hours (patient 2)
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