Short reports

This is an important as it illustrates the combination of an unusual site of gallstone impaction, which was not diagnosed in life, and the effects of age, delay in seeking medical care, and concomitant previously undiagnosed disease leading to fatality. We believe it to be only the third reported case of gastric outflow obstruction by a gall stone and the first combined with non-insulin dependent diabetes mellitus causing death by this complex metabolic derangement.

Systemic reactive amyloidosis associated with Castleman's disease: serial changes of the concentrations of acute phase serum amyloid A and interleukin 6 in serum

Shu-ichi Ikeda, Hisanao Chisawa, Seiji Kawasaki, Junko Ozawa, Yoshinobu Hoshii, Tadaaki Yokota, Tunet Aoi

Abstract
A case is reported of a 21 year old woman who suffered from Castleman's disease and systemic reactive amyloidosis. The serum concentrations of serum amyloid A (SAA) and interleukin 6 (IL-6) were extremely high and amyloid protein was immunohistochromically identified as AA. After surgical excision of a large retroperitoneal lymph node with the pathological findings of plasma cell type of Castleman's disease, both serum SAA and IL-6 declined, showing a similar pattern of reduction curves. All clinical symptoms and laboratory abnormalities greatly improved. The biochemical feature of Castleman's disease is abnormal production of IL-6 and this cytokine continuously may stimulate the synthesis of an amyloid precursor, SAA, causing systemic reactive (AA) amyloidosis. This pathogenic theory is strongly supported by the present study.

Keywords: Castleman's disease; amyloid; serum amyloid A; interleukin 6

Systemic reactive (AA) amyloidosis usually occurs in patients with chronic inflammatory disorders. Serum amyloid A (SAA), which is an acute phase reactant of hepatic origin, is an amyloid precursor in this type of amyloidosis. It is well known that the serum concentration of SAA dramatically increases in the inflammatory state and this response is mediated by actions of some cytokines including interleukin 1 (IL-1), IL-6, and tumour necrosis factor (TNF).

Castleman's disease is a unique form of lymphoproliferative disorder characterised pathologically by the presence of giant lymph node hyperplasia with plasma cell infiltration. Patients with this disease commonly have fever, anaemia, hypergammaglobulinaemia, and an increase in the serum concentrations of acute phase reactant proteins, all of which are ascribed to the large amount of IL-6 produced in the hyperplastic lymph nodes. We examined serial changes of serum concentrations of SAA and IL-6 in a patient with Castleman's disease and systemic reactive amyloidosis who was treated with surgical removal of an involved large solitary lymph node.

Case report
The patient was a 21 year old woman with a nine year history of general fatigue, arthralgia, and slight fever. In the past three years she had been suffering from epigastric discomfort and poor appetite. On examination, she looked sick and had an enormously enlarged liver with hard consistency, other physical findings were unremarkable. Abnormal laboratory findings are summarised in table 1. Briefly, she had a raised erythrocyte sedimentation rate (152 mm in the first hour), raised C reactive protein (CRP), anaemia, thrombocytosis, hypoalbuninaemia, hypergammaglobulinaemia, and slight proteinuria. Biopsies of liver tissues and gastric mucosa showed severe amyloid deposits with alkaline Congo red staining: amyloid deposition diffusely involved the parenchymal sinusoidal space of Disse and this was also seen in the lamina propria and muscularis mucosae of the gastric mucosa. After pretreatment with KMnO4, these amyloid deposits lost the affinity for Congo red dye (data not shown). Computed tomography of the abdomen revealed a mass with small calcifications that mimicked a liver tumour in the caudate lobe. Surgical

Table 1 Laboratory findings in a patient with Castleman's disease and systemic reactive amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>Before operation</th>
<th>Nine months after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>12700</td>
<td>6620 µl</td>
</tr>
<tr>
<td>Red blood cell count</td>
<td>335 × 10^6</td>
<td>365 × 10^6 µl</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>6.2</td>
<td>9.4 g/dl</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>23.2</td>
<td>29.8%</td>
</tr>
<tr>
<td>Platelets</td>
<td>84.1 × 10^9</td>
<td>22.7 × 10^9 µl</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>16.9</td>
<td>14.2 s (10.0–12.0)</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>60.3</td>
<td>39.8 s (24.0–37.0)</td>
</tr>
<tr>
<td>Floxigen</td>
<td>836</td>
<td>427 mg/dl (155–300)</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>13.7</td>
<td>0.44 mg/dl (&lt;0.1)</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.3</td>
<td>4.5 g/dl (4.1–5.2)</td>
</tr>
<tr>
<td>γ Globulin</td>
<td>3.6</td>
<td>1.9 g/dl</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>13</td>
<td>22 mg/dl (9–22)</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Negative</td>
<td>Not examined</td>
</tr>
</tbody>
</table>

Numbers in parentheses are normal values.

exploration disclosed an isolated extrahepatic mass (6.2 × 4 cm in size) that was located in the portocaval space; the pathological examination of the resected mass showed the characteristic findings of plasma cell type of Castleman's disease (fig 1A). The gall bladder remover at operation showed amyloid deposits mainly on the vascular walls and this amyloid was specifically immunolabelled with an anti-AA antibody (Dako, Glostrup, Denmark) (fig 1B).

For the first month after surgery the patient suffered from discharge of a large amount of chylaceous ascites (maximum about 4.2 l/day); to compensate for this body fluid loss fresh frozen plasma was transfused. Except for hepatomegaly, many clinical symptoms disappeared and all abnormal laboratory data had improved within nine months of surgery (table 1).

CHANGES OF SERUM SAA AND IL-6

Serum SAA concentration was determined under standard assay conditions using a latex agglutination kit (Eiken Chem Co, Tokyo, Japan) and the measurements of TNF, IL-1, and IL-6 were carried out by standard enzyme immunoassays in a commercial laboratory (SRL, Tokyo, Japan). Before surgery, IL-1 and IL-6 were undetectable in the patient's serum but the concentrations of both SAA and IL-6 were extremely high (SAA, 471.0 µg/ml (normal < 8 µg/ml); IL-6, 80.1 pg/ml (normal < 4 pg/ml)). After removal of a diseased lymph node concentrations of SAA and IL-6 decreased, and both values were near normal at the final examination (SAA, 7.1 µg/ml; IL-6, 5.4 pg/ml) (fig 2).

Discussion

In this patient a localised retroperitoneal mass was histologically demonstrated to be due to Castleman's disease, and concomitant systemic amyloidosis that presented as marked hepatomegaly was determined to be reactive amyloidosis on the basis of histochemical and immunohistochemical reactivities of tissue amyloid. Castleman's disease is an atypical lymphoproliferative disorder accompanied by severe chronic inflammatory responses. It has been shown that B cells in germinal centres of hyperplastic lymph node continuously produce excessive IL-6 and this cytokine is responsible for the variety of clinical symptoms and laboratory abnormalities in patients with this disorder.5,6

Recently, a small number of patients with Castleman's disease were reported to develop systemic reactive amyloidosis7,8 and the sustained high concentration of IL-6 in the sera of these patients seemed to play a causal role in the pathogenesis of this type of amyloidosis. It has been shown that IL-6 is a major hepatocyte stimulator and produces a variety of acute phase proteins in the liver of experimental animals and in cultured human hepatocytes,
SAA and CRP being most induced.\textsuperscript{10} In our patient the serum concentrations of SAA and IL-6 were very high and both values decreased in a similar pattern after surgical treatment of a primary lesion. In chronic inflammatory diseases several diverse kinds of cytokines have been considered to promote the abnormal production of SAA that eventually might lead to the development of systemic reactive amyloidosis. The present study has clearly shown that in the non-inflammatory state of Castleman's disease, only IL-6 is a critical regulator for the secondary occurrence of systemic reactive amyloidosis.

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Unusual eosinophilia not detected by an automated haematological analyser in a patient with liver cirrhosis

O Kabutomori, Y Iwatanai

Abstract

The use of automated haematological analysers to differentiate leucocytes has become more widespread. Unusual eosinophilia in a 57 year old man with liver cirrhosis, caused by hepatitis C infection, and abnormal blood counts detected using a manual method (eosinophils, 50%) was not detected by an automated analyser using the electrical impedance method (0.3%) or the optical method (14.1%). It is important to check blood films when cell counts are apparently abnormal, even for automated haematological examination. (J Clin Pathol 1997;50:965–969)

Keywords: eosinophilia; cirrhosis; automated haematological analyser

In routine work we assess complete blood cell counts and leucocyte differentials with an automated haematological analyser using the electrical impedance method\textsuperscript{*} (NE-8000; Toa Electric Co, Kobe, Japan). In addition, we check blood films manually to determine whether there are morphological abnormalities when the data from the automatic analyser are beyond the normal ranges (white blood cells (WBC) > 15.00 x 10\textsuperscript{9}/l or < 2.00 x 10\textsuperscript{9}/l; neutrophils > 80% or < 40%; lymphocytes > 60%; monocytes > 15%; eosinophils > 10%; basophils > 3%; red blood cells (RBC) > 6.00 x 10\textsuperscript{12}/l or < 2.00 x 10\textsuperscript{12}/l; mean corpuscular volume > 100 fl or < 70 fl; mean corpuscular haemoglobin > 35.0 pg or < 25.0 pg; mean corpuscular haemoglobin concentration > 35.0 g/dl or < 30.0 g/dl; platelets > 500 x 10\textsuperscript{9}/l or < 50 x 10\textsuperscript{9}/l) or beyond the delta check limits (WBC, 40%; neutrophils, 50%; RBC, 20%; platelets, 30%).

Case report

We encountered a case with unusual eosinophilia according to manual detection that was not detected by the automated haematological analyser using the electrical impedance method. The patient was a 57 year old man with liver cirrhosis caused by hepatitis C virus infection. Haematological data shown by the automated analyser was: WBC 3.75 x 10\textsuperscript{9}/l;

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & Impedance (%) & Optical (%) (THM5-HZ) & Manual (%) & Reference (%) \\
\hline
Neutrophils & 73.0 & 16.6 & 32 & 40–73 \\
Segment & & & 18–52 \\
Lymphocytes & 10.4 & 9.6 & 11 & 3–10 \\
Monocytes & 16.0 & 11.6 & 5 & 0–7 \\
Eosinophils & 0.3 & 14.1 & 50 & 0–2 \\
Basophils & 0.3 & 0.1 & 1 & 0–2 \\
\hline
\end{tabular}
\caption{Leucocyte differential determined by three different methods in the patient with liver cirrhosis}
\end{table}

\textsuperscript{*}18.8% of this lymphocyte fraction was classified as large unstained cells.