In healthy adults, most of the alkaline phosphatase (ALP) activity in serum (1) derives from liver ALP and bone ALP (2). Neutrophil ALP (NAP) is detectable in differentiated neutrophils and monocytes (3) and is the product of the liver/bone/kidney-type ALP gene (4). NAP mRNA and enzyme activity are induced by treatment of neutrophils with granulocyte colony-stimulating factor (G-CSF) in vitro (5); however, neutrophils are not usually identified as the source of increased serum ALP activity. Here we present data from several patients in whom neutrophils appeared to be a source of increased ALP activity.

Serum ALP activity was measured by the method of the Japanese Society of Clinical Chemistry (6). Serum ALP isoenzymes were separated electrophoretically with Titan III supporting media (Helena Laboratories). The serum ALP activity was correlated with the leukocyte count (Spearman r = 0.69; P < 0.001) and with segmented neutrophil count (r = 0.75; P < 0.001; Fig. 1).

We analyzed the correlation of serum ALP activity (and isoenzyme pattern) with the total leukocyte count and segmented neutrophil count in 14 additional patients with leukocytosis (Table 1 of the online Data Supplement). Correlations were highest in patients with polycythemia vera (PV), lung cancer (LC), or malignant lymphoma (ML), but we found no significant correlations in patients with chronic myeloid leukemia (CML), acute myeloid leukemia, acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome. The serum ALP isoenzyme patterns in the former cases showed bone-type dominance, whereas those in the latter cases showed liver-type dominance. The former cases did not have pathologic conditions with increased bone-type ALP caused by regenerative osteoblastic activity. Representative correlations for patients with PV, LC, ML, or ALL are shown in Fig. 2 of the online Data Supplement.

Increased NAP activity in some myeloproliferative diseases, such as PV, is related to the presence of increased numbers of AP transcripts (5). Granulocytes from healthy individuals and patients with PV or CML preferentially express bone-type ALP transcripts (7). In the neutrophils of healthy individuals, ALP is localized predominantly to the secretory vesicles. NAP activity is substantially decreased in hematopoietic stem cell disorders such as CML and paroxysmal nocturnal hemoglobinuria (2). NAP appears not to be involved in serum ALP activity in healthy individuals; however, both the protein concentration and the enzyme activity increase in cases of bacterial infec-

References

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DOI: 10.1373/clinchem.2005.053819

Table 1. Median breast milk GGT activity over 6 months.

<table>
<thead>
<tr>
<th>Time after birth</th>
<th>n</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
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<tbody>
<tr>
<td>1 and 3 days</td>
<td>2</td>
<td>9686a</td>
<td>7291</td>
<td>12 080</td>
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<tr>
<td>1 week</td>
<td>6</td>
<td>12 613</td>
<td>3139</td>
<td>16 060</td>
</tr>
<tr>
<td>2 weeks</td>
<td>4</td>
<td>3608</td>
<td>1688</td>
<td>11 820</td>
</tr>
<tr>
<td>4 weeks</td>
<td>7</td>
<td>3000</td>
<td>1231</td>
<td>8300</td>
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<tr>
<td>3 months</td>
<td>9</td>
<td>942</td>
<td>343</td>
<td>2000</td>
</tr>
<tr>
<td>6 months</td>
<td>9</td>
<td>501</td>
<td>186</td>
<td>807</td>
</tr>
</tbody>
</table>

* Mean value shown because of small sample size.

To the Editor:

In healthy adults, most of the alkaline phosphatase (ALP) activity in serum (1) derives from liver ALP and bone ALP (2). Neutrophil ALP (NAP) is detectable in differentiated neutrophils and monocytes (3) and is the product of the liver/bone/kidney-type ALP gene (4). NAP mRNA and enzyme activity are induced by treatment of neutrophils with granulocyte colony-stimulating factor (G-CSF) in vitro (5); however, neutrophils are not usually identified as the source of increased serum ALP activity. Here we present data from several patients in whom neutrophils appeared to be a source of increased ALP activity.

Serum ALP activity was measured by the method of the Japanese Society of Clinical Chemistry (6). Serum ALP isoenzymes were separated electrophoretically with Titan III supporting media (Helena Laboratories).

A 68-year-old man (patient 1) with easy fatigability presented with leukocytosis (55.3 × 10⁹/L) and a high neutrophil count (88.5%). Serum ALP activity was 3052 U/L (reference interval for adults, 117–356 U/L) with 91% bone-type ALP. The serum ALP activity was correlated with the leukocyte count (Spearman r = 0.69; P < 0.001) and with segmented neutrophil count (r = 0.75; P < 0.001; Fig. 1).

We analyzed the correlation of serum ALP activity (and isoenzyme pattern) with the total leukocyte count and segmented neutrophil count in 14 additional patients with leukocytosis (Table 1 of the online Data Supplement). Correlations were highest in patients with polycythemia vera (PV), lung cancer (LC), or malignant lymphoma (ML), but we found no significant correlations in patients with chronic myeloid leukemia (CML), acute myeloid leukemia, acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome. The serum ALP isoenzyme patterns in the former cases showed bone-type dominance, whereas those in the latter cases showed liver-type dominance. The former cases did not have pathologic conditions with increased bone-type ALP caused by regenerative osteoblastic activity. Representative correlations for patients with PV, LC, ML, or ALL are shown in Fig. 2 of the online Data Supplement.

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In myelopoiesis, ALP production in neutrophils is induced by G-CSF, and NAP is released into the bloodstream, perhaps through leakage of ALP from damaged or dead neutrophils. Fossa et al. (9) reported leukocytosis and increased serum ALP in response to G-CSF treatment and suggested that increased serum ALP activity was related to release of the enzyme from the increased numbers of leukocytes. Neutrophils were reported to be the source of increased serum ALP activity in experiments in which G-CSF was administered to rats (10).

Our present results reflect a common phenomenon caused by disease, such as granulocytic leukemia or PV. We conclude that neutrophils may be an important source of increased serum ALP activity or bone-type ALP isoenzyme. Increased bone-type ALP should not be misdiagnosed as representing a pathologic condition, such as thyroid disease (hyperthyroidism), in which there is osteomalacia; hyperparathyroidism (either primary or secondary); chronic renal failure with renal osteodystrophy; diabetes mellitus with osteomyelitis; or metastatic cancer in which there is osteoblastic activity, such as prostate cancer. The present report describes indirect evidence that NAP might explain high bone-type ALP activity in patients without osteoblastic bone disease. Direct evidence is needed of the biochemical and immunochemical properties of ALP in the sera of patients with leukocytosis.

References