Secondary Amyloidosis and Gastrointestinal Stromal Tumors

A Case Report and Discussion of Pathogenesis

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A 69-year-old man presented to our institution with a prior diagnosis of “stomach cancer.” He was initially seen at another institution for an evaluation of microcytic hypochromic anemia. Blood work showed that the hemoglobin concentration was 7.9 g/dL (79 g/L) with a hematocrit of 23.8%. An upper gastrointestinal endoscopy showed 2 large gastric ulcers and an erosive esophagitis. Concurrent magnetic resonance imaging showed a 6.0 × 6.0 × 7.0-cm gastric mass in the greater curvature, extending to the splenic hilum and tail of the pancreas. A biopsy showed a spindle-cell neoplasm with a brisk mitotic rate and strong cytoplasmic staining with CD117 and CD34 reagents, consistent with a GIST. At our institution, radical proximal gastrectomy, splenectomy, partial pancreatectomy, left adrenalectomy, and retroperitoneal lymph node dissection were performed. Intraoperative assessment revealed a 10-cm ulcerating lesion in the posterior wall of the stomach, involving the tail of the pancreas and splenic hilum. The patient suffered from intraoperative hypotension but was discharged on postoperative day 10 in good condition. Six months later, he developed liver metastases, with histology and immunohistochemistry identical to the original gastric lesion.

MATERIALS AND METHODS

Sections from the gastric neoplasm, pancreas, spleen, adrenal gland, and associated lymph nodes were formalin fixed and processed in the usual fashion. Sections were stained with hematoxylin-eosin, CD117 (Dako Corporation, Carpinteria, Calif), CD34 (Ventana, Tucson, Ariz), amyloid A component (AA) (Dako), and Congo red (Mallincrodt, Minneapolis, Minn).

RESULTS

Gross

The gastrectomy specimen harbored a 9.0 × 8.0-cm ulcer with an underlying 12 × 10-cm mass, with geographic necrotic foci. The tumor extended to the hilum of the 240-g spleen but did not infiltrate the splenic parenchyma. The neoplasm also extended to the superior surface of the pan-
Figure 1. A and B, Sections of the gastrointestinal stromal tumor (GIST) with immunostaining. A, Sections of the GIST show geographic areas of coagulative necrosis. Some nuclei appear somewhat epithelioid, whereas others are distinctively fusiform and spindled (hematoxylin-eosin, original magnification ×200). B, The tumor stains diffusely for CD117 (c-Kit) and shows a whorled architecture (CD117 immunostain, original magnification ×100).

### Table: Histochemical Staining Properties of the Tumor and Associated Organs*

<table>
<thead>
<tr>
<th></th>
<th>Light Microscopy</th>
<th>CD117</th>
<th>CD34</th>
<th>Congo Red</th>
<th>SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric tumor</td>
<td>GIST, no amyloid</td>
<td>(+)</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Spleen</td>
<td>Amyloid†</td>
<td>N/A</td>
<td>N/A</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>Amyloid†</td>
<td>N/A</td>
<td>N/A</td>
<td>(+)</td>
<td>Not performed</td>
</tr>
<tr>
<td>Liver</td>
<td>Metastatic GIST, amyloid</td>
<td>N/A</td>
<td>N/A</td>
<td>(−)</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

* SAA indicates serum amyloid A; GIST, gastrointestinal stromal tumor; and N/A, not applicable.
† Amyloid fibrils confirmed by electron microscopy.

creas without invasion. The adrenal gland was not grossly involved by the tumor. Lymph nodes measuring 0.4 to 2.3 cm were also identified.

**Microscopic**

The gastric neoplasm was composed of interlacing fascicles of spindle cells arranged in a whorled pattern (Figure 1). Mitotic figures were numerous, with 17 mitoses per 10 high-power field. Broad areas of geographic necrosis were identified. The tumor cells stained strongly for CD117 and CD34. Amyloid was not identified in either the tumor or the blood vessels in the underlying stomach. Gastric AA immunoperoxidase studies were negative.

The splenic parenchyma was completely replaced by glassy, amorphous red-pink material that stained with Congo red and showed apple-green birefringence with polarized light (Figure 2). The splenic amyloid also stained for AA. Similar amyloid deposits were seen in the adrenal gland and confirmed by electron microscopy.

Sections of the liver mass showed metastatic GIST and amyloid deposition; these findings were confirmed by Congo red.

**COMMENT**

The incidental discovery of secondary amyloidosis in conjunction with a GIST is rare. Recently, a single case of GIST with renal amyloid was reported. However, in contrast to the previous report, we documented extensive amyloid deposition in the spleen and adrenal gland. Even sections of the liver, taken at a later date to confirm the presence of metastatic disease, showed amyloid deposition. Congo red stains, immunohistochemistry (anti-AA), and electron microscopy all confirmed the presence of secondary amyloid. Renal amyloidosis based on clinical grounds was also suspected. Because this patient had neither hematologic malignancies nor clinical indications for primary amyloidosis, we believe that this case represents an instance of tumor-initiated secondary amyloidosis.

Secondary amyloidosis is a recognized complication of malignancy, and high circulating AA levels have been linked to gastric, colon, and rectal malignancies. A single case was reported of a woman with multiple endocrine neoplasia and a gastric “leiomyoma” with systemic amyloidosis. Another report documented a true high-grade GIST with renal amyloid. Thus, to our knowledge, our case is only the second to establish the association between malignant GISTs and extensive amyloid deposition.

An elevated serum AA (SAA) confirmed the secondary nature of the systemic amyloid deposition, illustrated by positive SAA immunostaining in the amyloid-infiltrated spleen. SAA is an acute-phase reactant and the circulating precursor of AA, the amyloid protein fibril that is ultimately deposited in various organs. SAA is synthesized by hepatocytes in response to inflammatory cytokines and its expression is regulated by complex mechanisms including interleukins and tumor necrosis factor. Because these inflammatory mediators potentiate serum levels of
SAA, we postulate that the extensive coagulative necrosis in our patient’s GIST induced a cytokine-driven inflammatory response that stimulated SAA production. The tumor-initiated inflammatory response prompted the hepatic production of SAA protein, resulting in AA deposition in both systemic vasculature and highly vascular organs such as the spleen, adrenal glands, and liver. Recent experimentation has shown that inflammatory cytokines inhibit monocyte-mediated SAA degradation in vitro, which underscores the importance of adequate SAA degradation and of the influence of cytokines in secondary amyloid deposition.

In contrast to the case previously described in the literature, we did not identify amyloid in either the tumor itself or the surrounding vasculature. Likewise, no amyloid was seen in the vessels of the adjacent uninvolved stomach, despite the use of both Congo red stains and electron microscopy to increase diagnostic yield. Immunoperoxidase tests for SAA in these locations were also negative. These findings were surprising, given the extensive degree of amyloid deposition in the spleen and adrenal gland. Such findings suggest that, although the tumor may mediate or initiate the production of SAA, it does not generate the amyloid directly, since amyloid was not found within the tumor proper. The literature supports the contention that the elevated SAA in patients with disseminated carcinoma was of hepatic origin rather than a tumor cell product. This, in turn, suggests that large, necrotic, rapidly growing GISTs with an exuberant inflammatory reaction are more likely to induce secondary amyloidosis, which is consistent with the high mitotic rate and zonal necrosis noted in the previously documented GIST-associated amyloidosis cases.

In summary, we have described a malignant GIST associated with systemic amyloidosis. Amyloid deposits were identified in the spleen, adrenal gland, and liver. To our knowledge, this is a rare association, with only 1 additional documented case. With the advent of CD117 immunostaining and increased recognition of this tumor, new cases may be more easily identified in the future.
prognostic significance of secondary amyloidosis is currently unclear. Both our case and the other documented case represent high-grade malignant variants, and the patients are more likely to die from their tumors than systemic amyloidosis. However, with the effective treatment of GISTs using Glivec, the management of secondary amyloidosis may gain increasing importance.

References