

## PSEUDOLYMPHOMAS OF THE SMALL INTESTINE

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Difficulty in the histopathological separation of atypical reactive hyperplasia of the lymphoreticular system from neoplasia is not new. Such difficulty has led to the nosological existence of peculiar tumors which have defied precise classification. Those occurring in the gastrointestinal tract have been designated "pseudoleukemia gastrointestinalis"<sup>1</sup>, "unclassified lymphoma"<sup>2</sup>, and "pseudolymphoma"<sup>3</sup>.

An awareness of these atypical appearing yet biologically benign tumors is important since their gross and histological appearance so often simulates a malignant lymphoma<sup>4</sup>. Whereas recent reports have recorded data concerning "pseudolymphomas" occurring in the stomach<sup>3</sup>, lung<sup>5</sup> and upper respiratory tract<sup>6</sup>, we have been unable to find similar reports relating to the small intestine.

It is the purpose of this report, with the presentation of three cases of pseudolymphoma of the small intestine, to: 1. Present a hypothesis regarding the pathogenesis of pseudolymphoma of the small intestine. 2. Proffer morphologic criteria for the recognition of these tumors in the small intestine. 3. Compare the biological behavior of pseudolymphoma with true lymphoma.

### CASE REPORTS

*Case 1:*—A 49-year old bartender was admitted to The University of Michigan Medical Center in May of 1950, following a short period of increasingly severe abdominal pain, nausea and vomiting. A gastrojejunostomy for peptic ulcer of the stomach had been performed nine years earlier.

Admission laboratory findings were all within normal limits. Emergency roentgenographic examination of the abdomen revealed obstruction of the small intestine (lower ileum).

The patient was in acute abdominal distress, manifesting a moderately tender and distended abdomen in which high-pitched bowel sounds could be heard. Cantor tube decompression relieved the patient's pain and abdominal distention, but withdrawal of the tube led to recrudescence of symptoms. Following a second decompression by Cantor tube, a celiotomy was performed.

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Thirty cm. from the ileocecal valve, a six cm. mass obstructed the small intestine. Regional lymph nodes were enlarged. The serosal surface of the intestine, at the point of the mass, was adherent to the pelvic floor, sigmoid colon and urinary bladder. An end-to-side anastomosis was performed after resection of the involved small intestine. Six thousand four hundred and fifty roentgens were administered to the lower abdomen and pelvis in the postoperative period.

A 14-year follow-up examination found the patient healthy and without any gastrointestinal complaints. Roentgenographic examination of the gastrointestinal tract demonstrated no evidence of residual disease.



Fig. 1—Pseudolymphoma in Case 1. Note sharp demarcation from uninvolved small intestine ( $\times 20$ ).

*Case 2:*—In February, 1960 a 64-year old public health nurse was admitted to The University of Michigan Medical Center because of persistent nausea, vomiting and colicky lower abdominal pain.

The patient first experienced colicky abdominal pain in 1951 and since 1957 had noted a change in the character of her stools. At first they were pale, yellow, and bulky, becoming foul smelling, buoyant and greasy in the months just prior to her admission. She described her pain as lower abdominal and sharp, associated with abdominal distention and often nausea and vomiting. Antacids, belladonna and sulfonamides brought no symptomatic relief.

Vital signs and examination were within normal limits except for abdominal distention, hyperactive bowel sounds, and diffuse abdominal tenderness. Hematologic and biochemical determinations including a glucose tolerance test were normal. Upper gastrointestinal x-ray studies disclosed diffuse mucosal changes in the small intestine consistent with regional enteritis and partial obstruction.

Celiotomy and resection of 30 cm. of small intestine and attached mesentery were performed. A three cm. nodular constricting mass was present in the distal portion of the resected small intestine. The patient was last seen in July, 1965, when thorough examination revealed no evidence of residual disease.

*Case 3:*—A 47-year old automobile inspector entered The University of Michigan Medical Center in December, 1961 following an episode of melena.

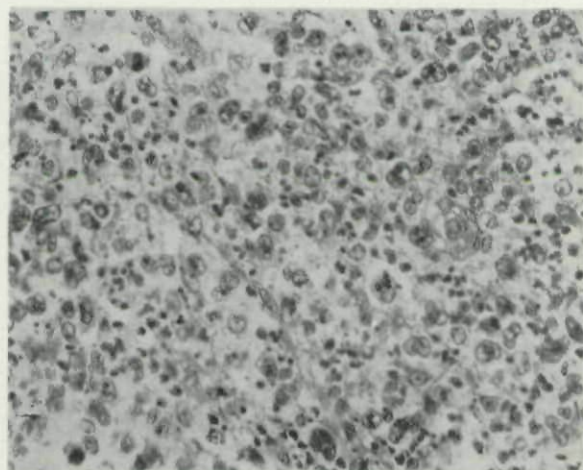


Fig. 2—Prototypic appearance of the pseudolymphomas manifested by all three patients of this report. Predominant cell is a large mononuclear cell in a polymorphous infiltrate. Note the prominent phagocytosis. Hematoxylin and eosin ( $\times 500$ ).

During the preceding four years, he had been twice hospitalized elsewhere for the investigation of abdominal pain. The pain was described as cramping and in the lower abdomen, and lasting for one to two hours. It always occurred after meals and recently had been associated with a firm, shifting abdominal mass, palpable by the patient. Relief was obtained by vomiting. Over the course of his illness he sustained a 22 pound weight loss. Extensive roentgenographic examinations on two occasions, including gastrointestinal series and cholecystograms, failed to disclose an abnormality.

Admission physical examination demonstrated only a slightly tender abdomen. No masses were palpated. Hematologic and biochemical studies were within normal limits. X-rays of the upper gastrointestinal tract disclosed "diffuse small bowel disease" with coarsening and partial obliteration of the mucosal

detail, especially in the duodenum and proximal small intestine. Following a short period of ineffective treatment, the patient developed signs and symptoms of partial small bowel obstruction and was subjected to celiotomy.

Two areas of intestinal involvement were discovered: the wall of the duodenum was thickened and the jejunum was dilated for three feet distal to the ligament of Treitz, at which point the luminal diameter was constricted. The small intestine was normal from this point until four feet proximal to the ileocecal valve. Here, the wall of the small intestine was again thickened. An ileojejunal resection and ileotransverse colostomy were performed.

Postoperative recovery was rapid and the patient went home 13 days after surgery. The patient was free of symptoms when last seen by physicians in July of 1964.

*Gross and microscopic descriptions of Cases 1, 2 and 3:*—An ileal mass, partially occluding the lumen of the small intestine, was present in the resected segments of small intestine from each of the three patients. The mass, in each instance, manifested fairly sharp demarcation from the adjacent small intestine (Fig. 1). In Cases 1 and 2 the gross configuration of the tumor was nodular with a diffuse infiltration through the wall of the small intestine. The lesion in Case 3 was nodular and showed ulceration of its surface. Fibrosis, thickening of the wall and subserosa, and enlargement of the adjacent lymph nodes were conspicuous findings in the last two patients.

The microscopic appearance of each *mass* was strikingly similar. The cellular infiltrate was not monomorphic, as in the usual lymphosarcoma or reticulum cell sarcoma, but rather was polymorphous (Fig. 2). The dominant cell was a large mononuclear cell possessing a high nuclear-cytoplasmic ratio and a vesicular nucleus in which the chromatin was clumped. Phagocytosis of nuclear debris by these and related cells, although focal, was a conspicuous feature. Admixed with this predominant cell (phagocytic or not), were lymphocytes, plasma cells, and eosinophils, the latter often appearing in clusters. Vascular proliferation was variable but in areas dominated the microscopic field. The adjacent lymph nodes manifested reactive hyperplasia. The small intestine adjacent to the masses in Cases 2 and 3 was the site of extensive submucosal and subserosal fibrosis, and marked reactive hyperplasia of the lymphoreticular apparatus. Fissure ulcers of the mucosa and pyloric metaplasia of intestinal glands were demonstrated. These alterations were entirely consistent with an underlying or coexistent regional enteritis (Fig. 3).

#### COMMENT

Certain disorders of the gastrointestinal tract may predispose to the development of neoplasia; ulcerative colitis, polyposis coli, and chronic gastritis have been most often implicated. Gough and his associates<sup>7</sup> have recently

suggested that celiac disease and idiopathic sprue should be considered "pre-malignant" with lymphoma arising as a complication of the long-standing alimentary tract disorders. Despite the chronicity of regional enteritis, the disease is rarely considered as a premalignant disorder. When one considers the *biological* progression of the disease, as manifested by histopathological appearances during various stages, atypical hyperplasia simulating lymphoma or true lymphoma itself, should not be an altogether unexpected reaction. The relationship of historical, clinical and histopathological evidence of a preceding and underlying regional enteritis in two of the three patients presented in this report serves to confirm this possibility.

Marshall<sup>8</sup> and others<sup>9</sup> consider regional enteritis to be a panhyperplasia of the reticular tissue of the small intestine (ileum), and occasionally of the colon

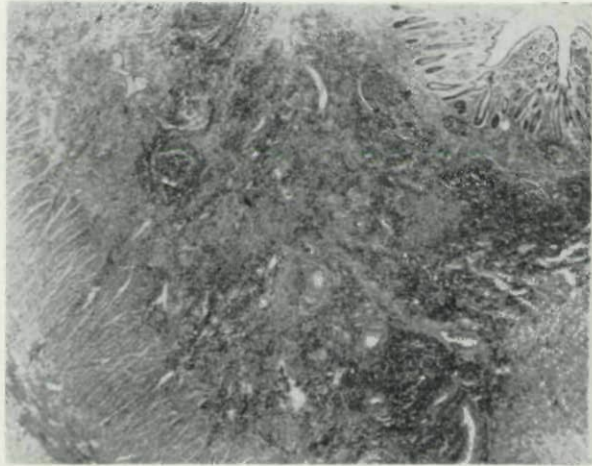


Fig. 3—Ileum adjacent to pseudolymphoma in Case 3, manifesting the histopathologic features of regional enteritis. Note the lymphoreticular hyperplasia, including fibrosis in the submucosa. Hematoxylin and eosin ( $\times 35$ ).

and the lymph nodes draining these areas. Fibrosis and cicatrization are the usual morphological end results of this hyperplasia of the reticular framework of the intestine. Uncommonly, however, the reaction is complex, and there is a deviation from the usual progression and maturation of tissue changes. Such a deviate reaction is characterized by an atypical lymphoreticular hyperplasia leading to the formation of a space-occupying mass in which the predominant cell is an atypical reticular stem cell. The gross and histological appearance of such a lesion may simulate a true lymphoma and we acknowledge the difficulty in differentiating between the two. Two of the three tumors of this report were originally diagnosed as "primary lymphoma, unclassified", of the small intestine. In deference to the hyperplastic yet atypical appearance of these tumors, the designation "pseudolymphoma" seems appropriate.

In accordance with Gough<sup>7</sup>, we contend that lymphoreticular tumors may arise as a result of chronic stimulation, such as occurs in sprue or regional enteritis. We differ, however, in that he has failed to recognize a benign variant to this expression. Of 18 cases of "lymphoma" and sprue<sup>10,11</sup>, there have been eight cases diagnosed as Hodgkin's disease<sup>10-15</sup>. In six of these eight cases<sup>10-13</sup>, the lesions were confined to the intestine and/or local adjacent mesenteric lymph nodes. Furthermore, death has not been ascribed to the dissemination of lymphoma in any instance. The validity of the histological diagnosis in such cases is difficult to accept when one considers that: 1. Hodgkin's disease is distinctly unusual as a "primary" lymphoma in the small intestine; less than 20 cases have been reported since 1949<sup>16-20</sup>, and 2. of all primary lymphomas in the small intestine, Hodgkin's disease has by far the worst prognosis. The majority of patients die of disseminated Hodgkin's disease *within* five years after the histological diagnosis and treatment<sup>16</sup>.

James Ewing was perplexed by gastrointestinal Hodgkin's disease, stating it was "ill-defined", warranting a separate classification since it differed so widely in structure and distribution from Hodgkin's granuloma<sup>21</sup>. He further recognized and acknowledged a group of locally destructive, *hyperplastic* lesions found especially in the stomach, ileum and cecum, which *resembled* Hodgkin's disease. Azzopardi and Menzies<sup>22</sup>, Jackson and Parker<sup>23</sup>, Dawson et al<sup>16</sup> and Salvesen and Kobro<sup>12</sup> have experienced the same difficulty in the histopathological diagnosis and classification of these atypical lesions. The similarity of pseudolymphomas to lymphomas and to Hodgkin's disease in particular, has no doubt led to their inclusion in those categories.

Three histopathological features serve to distinguish the pseudolymphomas from lymphomas: 1. Except for Hodgkin's disease, lymphomas are classically monomorphic, while pseudolymphomas are polymorphous in character. 2. Reed-Sternberg cells, the diagnostic cell of Hodgkin's disease, are not found in pseudolymphoma. 3. Unlike lymphomas, histological evidence of phagocytosis is present in pseudolymphomas.

There is very little in the clinical or operative findings which serves to differentiate pseudolymphomas from primary lymphomas of the small intestine<sup>24</sup>. Age and sex differences are negligible. Signs and symptoms of intestinal obstruction are common to both groups. A palpable mass, although occurring more frequently in patients with lymphomas, may be present in those manifesting a pseudolymphoma. The gross features of each may be so alike as to make their separation impossible. Both lesions occur most frequently in the distal small intestine. Two features may have importance in the differential diagnosis. The history of gastrointestinal "dysfunction" is longer in patients with pseudolymphoma than in patients manifesting a primary neoplasm. A clinical history and surgical findings consistent with coexistent regional enteritis favors a diagnosis of pseudolymphoma. Finally, while a diagnosis of primary lymphoma

of the small intestine is not incompatible with long life after proper treatment, recurrences are common, and death and/or extraabdominal dissemination is the rule.

#### SUMMARY

Pseudolymphomas are tumors arising as an expression of reactive hyperplasia of the lymphoreticular system in various organs. In the gastrointestinal tract, the stomach and distal small intestine are areas of predilection. Predisposing causes appear to be related to chronic alimentary tract disease, i.e., chronic gastritis, sprue, and in the cases herein reported, regional enteritis. Clinical symptoms and signs are similar to those manifested by patients with primary lymphoma of the small intestine. Differential diagnosis may be difficult and is dependent upon the recognition of the polymorphous character of the infiltrate. Clinical and pathological recognition of these atypical reactive lesions is important since their histological similarity to lymphoma, particularly Hodgkin's disease, has led to their inclusion as malignant lymphomas.

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#### ERRATUM

Through an error, Figures 3 and 4 on page 102 were printed upside-down in the article "Diffuse Esophageal Spasm" by Drs. Rider, Moeller and Puletti, which appeared in our August, 1965 issue.

We sincerely regret this error, and the correction has been made in the reprints.



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