NEUROBLASTOMA OF THE INTESTINE *

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Embryologists agree that the primitive undifferentiated nerve cells are of ectodermal origin, and early in the course of the histogenesis of the nervous system these cells differentiate into spongioblasts and neuroblasts. The former develop the supporting neuroglia structures of the central nervous system, while the latter are the precursors of neurons and also of the migratory cells which spring from the ganglionic crest, the anlage of the sympathetic nervous system. Some of these neuroblasts migrate ventrally toward the aorta to form the sympathetic chains with their paraganglionic structures and also invade the mesodermal part of the suprarenal glands to form their medullae. It is believed by some (Kohn ¹) that such primitive nerve cells may come to rest anywhere in the body, remain in a latent state and at some later time may proliferate and become neoplastic.

Marchand, in 1891,² reported a tumor of a suprarenal gland in a child 9 years old, which was rich in cells and fibrils, resembling the tumor now recognized as neuroblastoma. The presence of the fibrils led him to consider it a glioma.

Küster, in 1905,³ reported two similar cases; one, a child 3 months old, presented a primary tumor of the right suprarenal gland with metastases in the liver; and a second case in which the tumor was also primary in the suprarenal gland, not complicated by metastases. He described undifferentiated nerve cells associated with fibrils, the latter staining brown with Van Gieson's method. He was the first to draw attention to the occurrence of a peculiar cell-grouping, the so-called "rosette" formations. He considered these tumors malignant gliomata.

Wiesel,⁴ in the same year, called attention to the similarity between the cellular picture of the tumors described by Küster, and that of primitive sympathetic structures and of the medulla of the suprarenal gland.

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In 1910, J. G. Wright ⁵ reported four similar cases and definitely described the neoplasm as a neuroblastoma. He was able to demonstrate a very close similarity in its structure to the primitive sympathetic nervous system and the medulla of the suprarenal gland. This work was later confirmed by Landau.⁶

The latter reported three cases, and stressed the fact that the fibrils need not necessarily be present in these tumors. He believed that the more malignant the tumor, the fewer the fibrils and the more cellular its structure; and suggested that the younger the host, the more embryonic in character and more malignant is the tumor. He also showed that ganglioneuroma can be regarded as merely a more mature and more highly-differentiated form of neuroblastoma.

Pick and Bjelschowsky ⁷ conversely pointed out that malignant neuroblastoma is the unripe counterpart of ganglioneuroma and therefore named these tumors *ganglioma embryonale sympatheticum*.

Pick, in 1912 ⁸ brought the number of cases up to eighteen, including one of his own. He discussed the histogenesis and relation of this form of tumor to the primitive nerve cells, and drew attention to the fact that in maturing the cells differentiate into higher, more specialized forms, the ganglion and paraganglion cells. Further contributions to the subject of neuroblastoma with extensive reviews have been made by Wahl,⁹ Harbitz,¹⁰ Lehman,¹¹ and R. A. Lambert.¹² Wolbach and Morse, in 1918,¹³ brought the total number of undoubted cases up to twenty-nine, including three of their own. They, however, did not include the two cases published by Harbitz. Since then, only a few cases of this relatively rare neoplasm have been reported, Gunby,¹⁷ Anderson and Shennan,¹⁸ and J. H. Berner.¹⁹

The sites of primary occurrence in the reported cases were the suprarenal glands, sympathetic ganglia, retroperitoneal tissues, coccygeal gland, nose and uterus.

The observations to date have indicated that the term neuroblastoma must be reserved for tumors composed only of the undifferentiated type of nerve cell. On the other hand, tumors composed of ganglion cells with well-defined nerve fibers are called ganglioneuroma; and, since they are highly differentiated, are usually benign, in contradistinction to neuroblastoma. The third form of neurogenic tumor is the paraganglioma which is composed largely of chromaffine cells.²¹

Where mature ganglion cells have been found in typical neuro-

blastomata, they are to be regarded as forms in which partial transition has taken place from the primitive neuroblast to the mature ganglion cell. (Pick,⁸ Landau,⁶ Martius,¹⁴ Wahl,⁹ and Dunn.¹⁵)

Martius reported a rather unusual case in which the tumor presented two almost separate parts, one simulating neuroblastoma, the other a ganglioneuroma. Other authors have reported cases of ganglioneuroma in which there occurred inclusions or islands of neuroblastoma (Pick und Bielschowsky,⁷ Freund,¹⁶ Dunn,¹⁵ and others). Mixed neurogenic tumors containing all three elements of ganglioneuroma, neuroblastoma and chromaffine cells have been reported by Wahl⁹ and others.

The two cases of neuroblastoma which I wish to add to the series already reported are unique because of their location and origin. In both instances the tumor arose in the jejunum, presumably from the nerve cells of the intestinal sympathetic plexus (Meissner's and Auerbach's). A search of the literature has failed to reveal reports of the occurrence of neuroblastoma arising in the intestine either primarily or by extension. The relative rarity of neuroblastoma occurring in the adult is an additional feature of interest.

REPORT OF CASES

CASE 1. Patient H. A., a widow, 55 years old, was admitted to Dr. Brill's service at Mount Sinai Hospital, New York City, on March 1, 1924, complaining of increasing constipation for four months. She attributed her complaint to an accident which occurred in 1923, when she was struck by a taxicab and sustained an injury to her right hip. The constipation was obstinate and required drastic cathartics for relief. There were no abdominal pains nor cramps, no nausea, vomiting, jaundice or melena. Her stools were usually firm, formed and dark brown in color. She had lost about 30 pounds in the preceding four months. Her past history was essentially negative. She had been a widow for twenty years and was never pregnant. There was no history of operations or serious illnesses. She had passed the climacterium twelve years ago.

Physical examination on admission to the hospital showed her to be well developed but markedly emaciated. There was moderate bilateral exophthalmos. The pupils reacted sluggishly to light. The heart was slightly enlarged and a systolic murmur was audible over the apex. The abdomen was distended. On palpation a large, oval, smooth, hard and immovable mass could be felt in the epigastrium, extending downward to the level of the umbilicus, more to the right than to the left of the midline. There was marked generalized voluntary rigidity of the abdominal muscles. The genitalia, aside from marked senile atrophic changes were negative. Examinations of the stools gave repeated positive guaiac reactions. The blood count, blood Wassermann test, and blood chemistry were negative. The phenolphthalein test revealed excretion of 80 per cent of the dye in the urine in two hours. Roentgen ray examination of the

colon with the aid of a barium enema showed the sigmoid to be markedly compressed by an extrinsic intra-abdominal mass.

An exploratory laparotomy by Dr. J. Brettauer disclosed a large neoplastic mass, densely adherent to the anterior abdominal wall. On separating the adhesions as well as the adherent omentum from the upper aspect of the tumor, the latter was brought into full view. The mass was about 8 cm. in diameter, grayish in color and had a rough surface. It appeared to occupy the upper portion of the mesentery and in it were incorporated loops of the upper portion of the jejunum. The large intestine encircled the mass, but was not invaded by it.

Five days after the exploratory laparotomy, the patient died from an extensive postoperative bronchopneumonia.

Necropsy. The body was that of an emaciated woman 55 years of age. Rigor mortis was complete. No icterus or petechiae were present. A 15 cm. median, recent abdominal operative incision was present which had been closed with interrupted sutures. Upon opening the peritoneal cavity a large, oval, firm, grayish-white, neoplastic mass measuring 15 x 10 cm. in diameter was found, which involved several loops of jejunum 5 cm. distal to the fossa duodeno-jejunalis and the contiguous mesentery. There were many recently formed fibrous adhesions between the parietal peritoneum of the anterior abdominal wall, omentum and the anterior surface of the neoplasm. The tumor apparently arose in the wall of the jejunum and by direct extension involved the walls of several adjacent loops of the jejunum and extended backward, distorting and invading the mesentery and the mesenteric lymph nodes in this region for a distance of about 5 cm. from its main attachment. As the result of erosion of the walls of the adjacent loops of intestine by the invading neoplasm, an intercommunication was established among several loops of the jejunum so as to form a cavity, the wall of which was formed partly by intestine and partly by tumor. The anterior surface of the mass, after separation of fibrino-purulent omental adhesions, was found to be greenish-yellow in color and necrotic in places. The free surface of the cystic cavity of the neoplasm was thrown up into large, firm, salmon-pink colored, irregular excrescences, covered by a film of thick mucus. Here and there necrotic areas were found. Cut section of solid portions of the tumor presented a homogenous, pinkish-white, friable surface.

The duodenum and the jejunum proximal to the site of the neoplasm were widely dilated, due to partial constriction of the lumen of the jejunum at the site of the neoplasm. The distal portion of the jejunum and the ileum were collapsed. The large intestine encircled

the neoplasm without being involved in the growth. On the basis of gross observation a tentative diagnosis of sarcoma of the intestine was made (Figs. 1 and 2).

The lungs were the seat of an extensive postoperative bronchopneumonia. The suprarenal glands were normal.

Examinations of all other organs revealed no significant findings.

Microscopic anatomy. Microscopic study of the tumor shows it to be essentially composed of numerous small, round, "lymphoid" cells, containing deeply stained nuclei, rich in chromatin granules and surrounded with a very little cytoplasm. Scattered throughout the microscopic field, a fine fibrillar stroma is seen which stains brown with Van Gieson's method but does not give the characteristic neuroglia stain with Mallory's hematoxylin phosphotungstic acid method. The cells present an alveolar arrangement and here and there are polarized in double rows about a central mass of finely granular material, assuming characteristic "rosette" formations. Some of the cells are somewhat larger in size and show mitotic figures. An occasional giant cell can also be seen. A few pyriform cells are present whose cytoplasm extends outward in the form of delicate fibrillar processes. No mature ganglion cells can be found. Numerous thin-walled blood vessels are seen in the reticular network supporting the cellular elements (Figs 3 and 4).

The microscopic characteristics of this tumor led us to group it with the undifferentiated type of neuroblastoma. This diagnosis was concurred in by Dr. F. S. Mandlebaum and by Prof. Ludwig Aschoff who examined the sections during his recent visit to New York City.

CASE 2. Patient, J. F., white, male, Russian, 64 years old, was admitted to Mount Sinai Hospital on December 17, 1924, service of Dr. A. A. Berg. The patient had complained of severe epigastric pains and distress for several months with loss of weight and occasional vomiting. There was marked constipation. No hematemesis or melena had been observed.

On physical examination the patient was found to be markedly emaciated. His heart was slightly enlarged and the sounds were of poor quality. An indefinite resistance was felt in the left hypogastric region, but no distinct tumor mass could be palpated.

Roentgen ray examination of the gastrointestinal tract revealed a partial obstruction high up in the small intestine. The stomach was negative except for slight residue after six hours.

On December 12, 1924, an exploratory laparotomy was performed, under local anesthesia, by Dr. Berg. He found a neoplasm involving the jejunum commencing about 7.5 cm. from the fossa duodeno-jejunalis and extending dis-

tally in the wall of the intestine for a distance of 8 cm. There were metastases in the adjacent mesenteric lymph nodes. Many small metastatic nodules were present on the serous surface of the jejunum, just adjacent to the main tumor. Twenty-two centimeters of the jejunum were resected together with a portion of the mesentery, containing tumor and enlarged glands. An end to end anastomosis was then made in the usual manner. The omentum was sutured over the anastomosis with interrupted catgut sutures and the abdomen closed without drainage.

The patient made an uneventful recovery. His appetite increased and his bowels moved without catharsis. His general condition improved very rapidly and he was discharged from the hospital on July 18, 1924.

The macroscopic specimen consisted of a portion of jejunum which measured 22 cm. in length and 9 cm. in its widest diameter, the narrowest diameter being 4 cm. Attached to the serosal surface infiltrating the mesentery and wall of the intestine there was a cellular growth measuring 5 x 2.5 cm. This neoplasm was situated directly opposite the narrowest portion of the jejunum, namely the area which measured 4 cm. in diameter. It involved the wall of the intestine at this point and extended distally for a distance of 8 cm. The mucosa of the involved portion of intestine was irregular, nodular and firm. On the serosal surface there were several small, round or oval, firm, neoplastic elevations which on section were similar to the main neoplasm (Figs. 5 and 6).

Upon microscopic examination the tumor is found to be made up of small, round "lymphoid" cells whose nuclei stain deeply and contain chromatin granules. The stroma of the tumor is composed of a fine, irregular, diffuse, fibrillar network which does not give the characteristic neuroglia stain. Scattered throughout the microscopic field are many pyriform-shaped cells with a round base, and pointed apex which gives off a fine fibrillar process. Their deeply staining nuclei are oval in shape, vesicular in character and contain many chromatin granules. Many giant cells of variable sizes are also present, some of which show mitotic figures. They are not of the foreign body variety (Fig. 7).

An interesting point in the histological structure is its resemblance to spongioblastoma, a form of neoplasm derived from the primitive glial elements of the central nervous system described by Strauss and Globus.²⁰

SUMMARY

Two cases of intestinal neoplasma are reported. They are grouped with the neuroblastomata because of their histological characteristics.

In both instances the tumors arose in persons past middle age. Metastases were found only in the adjacent mesenteric lymph nodes. The relatively benign character, at least in one of the tumors (Case 2), may, perhaps, be explained by its histologic resemblance to a form of tumor designated as spongioblastoma.^{20, 21}

The observations indicate a new and hitherto undescribed site for primary neuroblastomata. So far as can be ascertained, no similar cases have been reported in the literature.

These cases emphasize the necessity for careful histologic study of atypical tumors, which on first examination might appear to be sarcomatous in character. It is probable that for this reason other instances of neuroblastoma of the intestine have been classified as sarcomata.

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DESCRIPTION OF PLATES LXXXIX-XCI

- Fig. 1. (Case 1.) Anterior view of intestinal tumor showing its origin and relations.
- Fig. 2. (Case 1.) Undersurface of tumor showing also partial obstruction of the intestine.
- Fig. 3. (Case 1.) Photomicrograph of tumor showing "lymphoid" cells containing deeply stained nuclei surrounded by very little cytoplasm. Cells present an alveolar arrangement. A fine fibrillar stroma is scattered throughout the field. (High power.)
- Fig. 4. (Case 1.) Section showing typical rosette arrangement of cells. (Higher magnification.)
- Fig. 5. (Case 2.) Drawing of specimen of tumor of jejunum; view of mucosal surface.
- Fig. 6. (Case 2.) Serous surface of tumor of jejunum with adjacent portion of invaded mesentery and lymph nodes.
- Fig. 7. (Case 2.) Photomicrograph of section of tumor showing presence of large numbers of giant cells and numerous pyriform-shaped cells alternating with small "lymphoid" cells. For detailed description see text.

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