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MINI REVIEW

General Surgery Approach to Neurofibromatosis Cases

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Neurofibromatosis is one of the most common autosomal dominant tumor syndromes with 1: 3000 birth incidence and 1: 4000 prevalence [1]. Neurofibromatosis has three main forms, clinical and genetic. Von Recklinghausen disease or Neurofibromatosis is the most common known as type 1 (NF-1). Neurofibromatosis type 2 (NF-2) and Schwannomatosis are two other forms [2]. Intraabdominal symptoms (gastrointestinal or retroperitoneal) are usually associated with NF-1. Abdominal neoplasms occurring in NF-1 patients can be examined in 5 categories: Neurogenic tumors, neuroendocrine tumors, non-neurogenic tumors, embryonal tumors and other tumors [3] (Table 1). This section summarizes the most important intra-abdominal findings of neurofibromatosis patients and their approach to general surgery.

Gastrointestinal symptoms in NF-1 patients have been well described and many cases have been reported; the true frequency of gastrointestinal tumors and the extent to which these have become clinically relevant are not fully known. Based on previous studies, it is estimated that 10% to 25% of patients with NF-1 have gastrointestinal tumors but less than 5% are associated with symptoms [4]. NF-1 gastrointestinal symptoms usually occur during middle ages or at a later age. Early diagnosis of abdominal findings associated with NF-1 disease is necessary to prevent serious complications associated with the tumor and to treat it appropriately [5].

Neurogenic Tumors

Neurofibromas and plexiform neurofibromas

Neurofibromas are the most common neoplasms in the abdominal cavity and retroperitoneum in NF-1 patients. Paraspinal, sacral or mesenteric sites are common. Neurofibromas of the gastrointestinal tract originating from the myenteric plexus are multiple polypoid lesions. Although usually asymptomatic (65%); pain, palpable abdominal mass and obstruction may occur when they are of gastrointestinal or mesenteric origin and contain mucosal bleeding. Rarely, neurofibromas may include other structures such as the liver and the genitourinary system. Plexiform neurofibromas are typical of NF-1 and can be transformed into Malignant

Table 1: Abdominal neoplasms of neurofibromatosis.

Neurogenic Tumors
Neurofibromas
Plexiform Neurofibromas
Malignant Peripheral Nerve Sheath Tumor
Ganglineuroma
Neuroendocrine Tumour
Carcinoid Tumor
Pheochromocytoma
Paraganglioma
Periampullary neuroendocrine tumors (Insulinoma, Glucagonoma, Somatostatinoma)
Non-Neurogenic Tumors
GIST
Embryonal Tumors
Neuroblastoma
Wilms Tumor
Rhabdomyosarcoma
Other Tumors
Adenocarcinomas
Extra-abdominal tumors (leukemia, lymphomas)

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Peripheral Neural Sheath Tumor (MPNST). Plexiform neurofibromas are characterized by their fascicular structure and are characterized as ''ring-like'' patterns [5]. Plexiform neurofibromas developing in retroperitoneum are bilateral, typically symmetrical lesions originating from the paraspinal areas. Surgical treatment aims to relieve the symptoms caused by pain, bleeding, obstruction and compression of other structures. In addition, surgical removal of plexiform neurofibromas prevents local infiltration and malignant transformation. In these tumors, the surrounding tissues and organs that are infiltrated in the intraabdominal and retroperitoneal areas should be removed with the tumor and the unblock must be definitively removed [6]. Such neurofibromas are difficult to exclude because they originate from the involvement of all neural plexuses and surrounding structures. Because of the risk of malignant transformation, radiotherapy is not preferred. If radical resection is not possible, debulking surgery should be performed to relieve palliative and compressive symptoms. Because of the presence of 75% high progesterone receptors of neurofibromas [7], the potential role of antiprogesterone therapy is suggested; randomized controlled studies have been conducted to explain the role of farnesyltransferase inhibitor and pirfenidone on treatment [8].

Malignant peripheral neural sheath tumor

Malignant peripheral neural sheath tumor (MPNST) is a tumor that develops from nerve tissue. MPNST is very rare cases occurring in 0.001% of the general population. Approximately 25-50% of MPNST cases are associated with NF-1 [9]. The first sign of MPNST is a mass or swelling that increases in size and sometimes causes pain or tingling sensation [10]. MPNST can be considered as an aggressive tumor because of the recurrence rate of 65% [10,11] after surgery and the risk of metastasis (most common lung) by 40% [12-14]. Surgical intervention is a radical resection of the tumor. If radical resection is not possible, palliative debulking surgery should be performed. Radiation therapy can be used to reduce the risk of relapse. Chemotherapy can be used in the preoperative period to reduce tumor size, to treat metastasis, and to remove the entire tumor during surgery.

Ganglioneuromas

Ganglioneuromas are polypoid benign tumors originating from the sympathetic ganglia, well-defined along the paravertebral sympathetic plexus, or in the adrenal gland or rarely in the gastrointestinal tract. They are also known as neuroblastic or neurogenic tumors [15,16]. They can grow in the presence of sympathetic nerve tissue and often in the abdominal cavity. Widely used in the adrenal gland, paraspinal retroperitoneum (sympathetic ganglia), posterior mediastinum and head and neck region; rarely, they are localized in the bladder, bowel wall, abdominal wall and gallbladder. Complete surgical resection is important for accurate diagnosis of ganglioneuroma, good tissue sampling and proper pathological examination of the specimen. In rare cases, the tumor may recur. Therefore, radiological examination is an important tool for appropriate localization and characterization of primary and recurrent tumors. Radiological examination can give an idea about the localization, shape and morphology of the tumor. The diagnosis cannot be based solely on radiological findings [17]. Therefore, complete excision of the tumor and pathologically appropriate tissue sampling are important steps.

Neuroendocrine Tumors

Carcinoid tumors

Carcinoid tumors originate from the Kulchitsky enterochromaffin cells in the bowel wall. Although the incidence of NF-1 patients increases, the prognosis is the same as the general population. The most common localization may be the appendix, but it can keep the entire gastrointestinal tract [18]. Often, abdominal pain, fever, vomiting, gastrointestinal bleeding and obstruction as well as rarely, such as diarrhea and flushing can be found with findings. Carcinoid tumors are usually solid polypoid or infiltrative lesions. In CT scan, it is difficult to differentiate carcinoids from the periampullary region from adenocarcinoma tumors; somatostatin analog scintigraphy can be helpful for differential diagnosis. NF-1-related carcinoid tumors tend to grow slowly, with a 5-year survey of 95%. Tumors less than 2 cm have a low risk of metastasis. Treatment of NF-1 dependent carcinoid tumors is not different from sporadic carcinoid tumors. Surgical resection should be performed due to the localization. Appendice carcinoids, appendectomy in tumors smaller than 1 cm is sufficient, 2 cm and larger tumors with peripheral lymph node dissection and right hemicolectomy should be done. In today's conditions, these operations can be performed either as laparoscopic or robotic [19]. Endoscopic transanal mucosal resection may be sufficient for tumors smaller than 1 cm in the rectum [20]. In other gastrointestinal and large tumors, palliative debulking surgery should be performed when the entire tumor is not removed. Targeted conventional chemotherapy should be planned in distant metastases or unresectable cases [21].

Pheochromocytomas

Pheochromocytomas are rare tumors of the adrenal glands in NF-1 patients. Although usually benign, it causes the release of stress hormones known as epinephrine and norepinephrine. Because of this reason; May cause symptoms such as hypertension, severe headache, anxiety, tachycardia, chest pain, nausea, vomiting, sweating, weakness. Rarely, when they occur outside the adrenal gland in the abdominal cavity, they are called

extra-adrenal pheochromocytoma or paraganglioma [22-25]. Pheochromocytomas may occur with some familial genetic syndromes [25]. The CT scan for diagnosis has a high sensitivity in identifying the homogenous and contrasted mass in the adrenal gland. MRI provides high specificity in differentiating it from other adrenal cortex tumors. In addition, 123-I-MIBG scintigraphy has high sensitivity and specificity to identify lesions.

Surgical resection of the tumor is the preferred treatment to normalize blood pressure values and prevent potential malignancy. In NF-1 patients, good exploration is mandatory for the possible presence of other neurofibromatosis-related tumors [26]. If exploration of the abdominal cavity tumor associated with NF-1, such as GIST, carcinoid tumor, neurofibroma, ganglioneuroma, etc., appropriate surgery should be planned.

Periampular neuroendocrine tumors

One of the characteristic symptoms of NF-1 in gastrointestinal system is periampullary region tumors. The symptoms of periampullary involvement include jaundice, cholangitis, pancreatitis, hemorrhage, and duodenal obstruction. Diabetes mellitus, dyspepsia and cholelithiasis are observed in somatostatinoma. Malignant and poor prognosis is associated with a high incidence of lymph nodes and liver metastases. Although periorbular adenocarcinomas can be mixed clinically and radiologically, the treatment is radical surgical resection [5]. Insulinoma and glucagonama are neuroendocrine tumors of the pancreas with an increased incidence with NF-1 disease. Similar procedures are applied with the treatment of sporadic neuroendocrine tumors. Curative treatments are possible with radical surgical resection. Operation procedure according to their localization is preferred as Whipple or distal pancreatectomy [27].

Non-Neurogenic Tumors

Gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors in the gastrointestinal tract resulting from Cajal cells of the myenteric plexus. The mean incidence is 55-65 years, and the most common localization is stomach (60%), ileum (30%), rarely duodenum (5%), colorectal region (4%) and more rarely esophagus. The incidence of GIST in NF-1 patients is more common and can be seen 4-25%. It is usually diagnosed in small intestine and can be diagnosed at an early age in multiple cases [28]. The most common localization of stromal tumors in NF-1 patients is stomach and jejunum. These tumors usually present with clinical signs of obstruction, bleeding, intussusception, volvulus or perforation.

Although it is rare in colon and rectum; stromal tumors in this localization may present with similar symptoms [4]. The most important prognostic factor in GIST is the mitotic index and the diameter of the tumor. The diagnosis can be made during an exploratory laparotomy for radiological examination or another operation [29]. In case of clinical suspicion; endoscopy, CT, MR and PET/CT can be diagnosed more clearly [30]. Surgical R0 resection was accepted as the gold standard; According to some authors, R1 resection may be accepted in certain localizations (duodenum, esophagus) which are considered high risk of surgical complication due to low risk tumors and high morbidity and mortality. As there is no tendency to metastasize to the peripheral lymph nodes, lymph node dissection is unnecessary [31].

In the case of diffuse or metastatic disease, tyrosine kinase inhibitors, such as imatinib, are preferred prior to surgery as a gold standard treatment with an 80% response rate. Both tyrosine kinase inhibitor and antiangiogenic factor, sunitinib, were approved as a new drug in the treatment. Today, even in the case of localized disease, studies are performed to take advantage of KIT inhibitors to avoid extensive surgical resection in the preoperative period [32].

Embryonic Tumors

Although the relationship between NF and Wilms tumors or neuroblastomas has been reported in the literature; not confirmed genetically or molecularly. Because of the recognized role of the NF-1 gene in the differentiation of muscle cells, the common pathogenetic mechanism between NF-1 and rhabdomyosarcoma is more prominent [28].

Other Neoplasms

It was determined that adenocarcinomas were able to retain the entire gastrointestinal tract in NF-1 patients. Since colon, esophagus, stomach and hepatobiliary tumors are common in the general population, the incidence is similar in NF-1 patients. Adenocarcinomas of the small intestine and periampullary region are more frequently seen in NF-1 patients when they encounter normal population. The surgical procedure performed according to the localization and stage of sporadic adenocarcinomas is also applied in NF-1 related adenocarcinoma tumors.

Other extra-abdominal tumors associated with NF-1 are leukemias and Non-Hodgkin's lymphomas [33]. As a result, intraabdominal symptoms and symptoms may occur when there is retroperitoneal and gastrointestinal involvement in NF-1. Given the haemorrhagic and obstructive complications of gastrointestinal tumors, possible symptoms and complications of pheochromocytomas and the risk of malignancy, early diagnosis of all these abdominal symptoms is of high importance. Multidisciplinary clinical evaluations are important in defining complications and neoplastic transformations.

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