RARE CLINICAL CASE OF JEJUNAL ANGIOMATOID FIBROUS HISTIOCYTOMA AND A LITERATURE REVIEW OF RADIOLOGICAL FINDINGS IN MALIGNANT AND NON-MALIGNANT TUMORS OF THE SMALL INTESTINE

Simonas Jesmanas[1], Ieva Čiučiulkaitė[1], Irina Gineikienė[2], Julius Vidikas[2]

[1]*Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[2]*Department of Radiology, Medical Academy, Lithuanian University of Health sciences, Kaunas, Lithuania*

Corresponding email: juliusvidikas@gmail.com

ABSTRACT

Background: Tumors of the small intestine represent a small fraction of gastrointestinal tract neoplasms and might be missed if the referring physician and radiologist are not actively looking for a tumor. The choice of an optimal imaging protocol for detecting tumors in the jejunum and ileum is crucial. The differential diagnosis should include both benign (GIST, lipoma, hemangioma, neural tumors) and malignant (adenocarcinoma, carcinoid, lymphoma and metastases) tumors. Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue tumor, and is never on the initial differential diagnosis of a small intestine tumor. In this article we present a case of jejunal AFH and a literature review of radiological findings in malignant and non-malignant tumors of the small intestine.

Clinical case: A 68-year-old male presented with a 1 month history of weight loss, lack of appetite, and pain in the right iliac and lumbar regions. Past medical history was significant for an adrenal tumor of unspecified origin and adrenalectomy in 2005. CT showed a non-homogenous infiltration located posterior to the ligament of Treitz and a polypoid exophytic mass. A biopsy was obtained during enteroscopy. Histological and immunohistochemical analysis confirmed an AFH. The adrenal tumor specimens were retrospectively re-analyzed and showed similar morphology and immunohistochemistry, therefore it was concluded that the neoplasm arose in the adrenal gland and metastasized to the jejunum.

Conclusions: In this report we presented to our knowledge the first case of an AFH of the adrenal gland which later metastasized to the jejunum.

AFH has several characteristic findings on MR imaging: a double-rim sign, fluid-fluid levels, and marginal infiltrating strings of tumor tissue.

To distinguish between benign and malignant tumors of the small intestine it is crucial to evaluate the number, location, vascularity, calcifications, growth and enhancement patterns, mesenteric and extra-intestinal involvement of the tumors.

Keywords: angiomatoid fibrous histiocytoma, small intenstine, small bowel, neoplasms, tumors, imaging, radiology

CLINICAL CASE

A 68-year-old male was admitted to our hospital on August 20, 2014 and presented with a 1 month history of 8 kg weight loss, lack of appetite and abdominal pain in right iliac and lumbar regions. Past medical history was significant for an adrenal tumor and a left adrenalectomy in 2005, and the histopathological examination of the excised lesion revealed uncertain histogenesis and malignancy. There were no significant findings on physical examination, except for pain in the right iliac and lumbar regions. Laboratory studies showed a microcytic anemia with a hemoglobin of 88 g/l and a mean corpuscular volume (MCV) of 71 fL, thrombocytosis with platelets of 555x109/l. C-reactive protein was elevated to 47, 7 mg/l.

Upper gastrointestinal tract (GI) barium contrast study showed two filling defects near the ligament of Treitz. Computed tomography (CT) of the chest, abdomen and pelvis revealed a mass located in the small intestine (Figure. 1).

Figure 1. CT of the abdomen with oral contrast showing a mass in the intestinal lumen producing a filling defect.
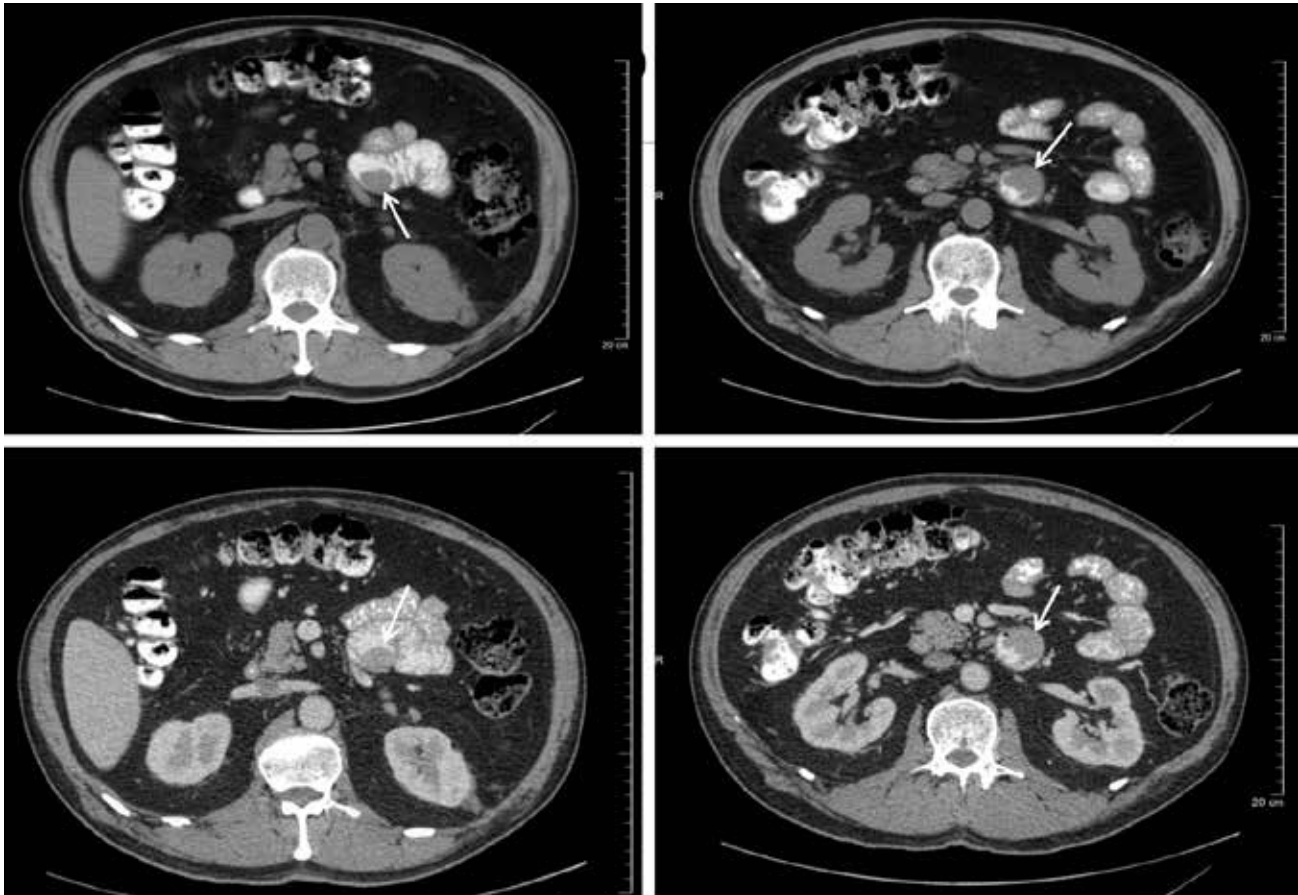
It was a non-homogenous infiltration up to 1.5 cm in depth with moderate contrast enhancement located posterior to the ligament of Treitz. In addition, just above this infiltration, a polypoid mass of about 1.7x1.4 cm growing exophytically directly into intestinal lumen, and a 4x0.9 cm possibly pathological lymph node in the mesentery were described. Based on this CT appearance, a small bowel neoplasm was suspected. Following the CT scan, the patient underwent enteroscopy to visually inspect the lesions. The procedure revealed two ulcerous lesions: one was near the ligament of Treitz and occupied a third of the lumen circularly, while the second was 4 cm below the ligament of Treitz and occupied two thirds of the lumen circularly.

Both lesions were biopsied during the procedure. Histological examination of the specimens revealed infiltration of the lamina propria by tumor cells. The cells had oval, polymorphic nuclei, indistinct cell borders and an eosinophilic cytoplasm. Mitosis was infrequent. Immunohis-

tochemistry demonstrated expression of desmin and epithelial membrane antigen (EMA). Aktin and CD56 were negative. Ki67 proliferative index was 30%. In addition, histological samples from 2005 were re-evaluated and the cells exhibited positive reactions with desmin, EMA and negative reactions with aktin, CD56, CK18. Ki67 proliferative index was 10%. Given the identical morphology and immunophenotyping, it was suspected that the primary adrenal tumor had spread into the small intestine. The diagnosis of angiomatoid fibrous histiocytoma was made based on studies of both specimens.

The patient underwent surgery to excise the duodenal and jejunal masses. Two pieces of material were removed. The first piece was composed of normal adipose tissue with a few fibrous tissue insertions.

The second piece consisted of two components. Macroscopically both excised components showed a circular serosa that was not overgrown. One component consisted of a firm mass with

atypical cells of moderate size with oval nuclei and various amounts of eosinophilic. Mitosis was infrequent. The Ki67 proliferative index was 70%.

Second component consisted of similar tumor cells, except that their nuclei were polymorphic and cells had a moderate amount of eosinophilic cytoplasm with indistinct borders. Blood-filled pseudoangiomatous spaces of variable size were prominent in the lesion. Ki67 proliferative index was 30%. The immunohistochemical stains were as follows: desmin - positive, aktin - negative, vimentin - positive, CD68 - negative, S100 protein – negative, CD56 - negative. All other markers were negative. Two lymph nodes with a diameter of 0,8 cm and 0,9 cm were also removed and demonstrated reactive changes.

DISCUSSION

ANGIOMATOID FIBROUS HISTIOCYTOMA (AFH)

Angiomatoid fibrous histiocytoma (AFH) is a particularly rare tumor of soft tissues which usually occurs in the dermis and subcutis of the extremities [1]. Most commonly, AFH arises in children and young adults and accounts for less than 1% of total soft tissue tumors [1-3]. AFH was first described by Enzinger in 1979 as a variant of malignant fibrous histiocytoma (MFH) with a tendency to occur in superficial tissues of the extremities and young age group, contrary to MFH which occurs in deep soft tissues of older individuals [1-3]. Today, AFH is classified as a distinct neoplasm due to its more favorable prognosis and benign clinical course [3-5].

Although most patients present with AFH in childhood, the age range is quite wide [6]. However, the mean age is approximately 20 years [4] and in most patients AFH occurs in the first 30 years of life [1, 6]. The most common site for AFH is superficial tissues of the extremities but rarely the tumor can arise in the trunk, head and neck [4]. There were several reported cases of AFH presenting in nonsomatic soft tissues which included the cranium, mediastinum, lungs, vulva, ovary, retroperitoneum, omentum and bone [7-8]. It is worth mentioning that our case reports the occurrence of AFH in the adrenal gland and small bowel for the first time.

Presentation of AFH is related to its location. Since the tumor tends to grow in superficial tissues, it mostly appears like a superficial nodular slowly growing mass. Pain and tenderness are possible but rather unusual symptoms of AFH. Typically, masses are found in those areas where lymph nodes are localized. Patients with AFH in other locations can present with symptoms related to affected organ or anatomical site. Patients with nonsomatic AFH are more likely to present with systemic symptoms than patients with somatic AFH. Fever, weight loss, general malaise, and anemia suggest that production of cytokines by the tumor is occurring. Also, the mean age of patients with nonsomatic AFH is higher by approximately 20 years [1-9].

The diagnosis of AFH is established after careful histopathological, immunohistochemical and cytogenetic examination because pre-operative diagnosis of AFH is hardly possible due to there being no specific clinical or imaging findings [9]. Macroscopically, AFH is usually a small tumor, the median size is just 2 cm, although tumor can grow to 10-12 cm [4]. The lesion is usually circumscribed, has a firm consistency and grey appearance. Microscopic examination often shows lesions with an incomplete pseudocapsule and in most cases surrounded by a "lymphoplasmacytic" infiltrate. AFH consists of sheets or short fascicles of round epithelioid or spindle cells. It is the only histological feature of AFH that remains constant in most cases [1]. The proportions of differently shaped cells may vary. Common features usually present in all tumor cells are bland, vesicular nuclei and a moderate amount of eosinophilic cytoplasm. Round cells have uniform nuclei and infrequent mitoses. Spindle cells can show nuclear polymorphism. This cellular morphology does not predict a worse outcome [10]. One more common finding is multifocal intralesional hemorrhage which contains blood-filled spaces of different sizes. Approximately two-thirds of lesions have this feature [1]. Hemosiderin deposits, accumulation of siderophages and sometimes giant cell formations can be prominent in the pseudoangiomatous spaces [10]. For the diagnosis of AFH immunohistochemistry provides only a supportive role because AFH

lacks a specific immunoprofile. Positivity for desmin, CD68 and CD99 can be demonstrated in approximately half of the cases. Three genetic abnormalities are related with angiomatoid fibrous histiocytoma: EWSR1–CREB1 fusion gene resulting from t(2;22)(q34;q12), FUS–ATF1 fusion gene resulting from t(12;16)(q13;p11) and EWSR1–ATF1 fusion gene resulting from t(12;22)(q13;q12) [10]. EWSR1–CREB1 is the most often discovered gene fusion in patients with AFH [11] and EWSR1–ATF1 is more often related to nonsomatic cases of AFH [7].

Treatment for angiomatoid fibrous histiocytoma is surgical resection. Wide local excision with adequate follow-up allow for successful management of the disease in a majority of patients. Local recurrence of AFH can occur in up to 15%, while AFH tends to metastasize in less than 5% of cases. AFH can recur due to either incomplete resection or the tumor being localized in the head and neck [1]. Both metastases and local recurrence in somatic AFH correlate with invasion into the deep fascia or muscle [4]. Nonsomatic AFH have higher local recurrence rate compared to somatic AFH. This may be due anatomical location which leads to difficulties in obtaining complete excision [7].

TUMORS OF THE SMALL BOWEL

Tumors of the small intestine represent a small fraction of gastrointestinal tract neoplasms and might be missed if the referring physician and radiologist are not actively looking for a tumor due to asymptomatic and non-specific nature of the disease or poorly taken medical history. Given these factors, it is likely that the small bowel will not be investigated with an optimal imaging modality and protocol for detecting neoplasms in jejunum and ileum. The situation is made even more challenging when physicians are faced with an unusual case as the one presented in this article. Thus, maintaining a high index of suspicion, devising an appropriate imaging protocol and knowing the differential diagnosis of small intestine neoplasms is crucial.

The small intestine makes up over 70% of the total length and 90% of the absorptive surface of the gastrointestinal tract. Despite its size, neoplasms in the small bowel have an incidence of only 1 per 100,000 people worldwide [12], which is about 3% of all gastrointestinal tract neoplasms [13]. Incidence is higher in Western countries than in Asia [14]. Over the past several decades the incidence of small bowel cancer has increased, with rates depending on the histological origin of the tumor: carcinoid tumors showed the highest increases in incidence compared with adenocarcinomas and lymphomas, while the incidence of sarcomas remained stable [15]. Currently about 30-40 % of small intestine tumors are adenocarcinomas, 35-40% are carcinoid tumors, 15-20% are lymphomas and 10-15% are sarcomas (gastrointestinal stromal tumors – GIST) [15-17]. The increase might be due to improved diagnosis with radiological and endoscopic techniques and the spread of not yet conclusively proven lifestyle or environmental factors [18]. Non-malignant tumors of the small intestine, which make up about 5% of all non-malignant gastrointestinal tumors, can be lipomas, adenomas, gastrointestinal stromal tumors (GIST), leiomyomas, hemangiomas, various neural tumors and hereditary polyposis syndromes, Peutz-Jeghers syndrome in particular [18-19]. Metastases to the small bowel are most common in metastatic melanoma [19, 24], but various other cancers may also involve the small bowel, most notably lung and breast from distal sites, ovarian and other GI primary tumors by intraperitoneal spread [19].

Possible radiological modalities used to investigate the small intestine include follow-through barium studies, fluoroscopy-guided enteroclysis, computed tomography (CT) or magnetic resonance imaging (MRI) with intravenous (IV) contrast, CT or MR enterography (bowel distention with oral contrast agents) and CT or MR enteroclysis (bowel distention with oral contrast agents delivered via naso-jejunal intubation). Capsule endoscopy is useful in evaluating the mucosal surface and detecting early tumors, but does not allow for visualization of the submucosa, outer wall of the bowel and adjacent structures like the mesentery [18-19]. After first line investigations of the gastrointestinal tract (ultrasound, endoscopy and barium studies), the most utilized modality is CT, which has an 80% sensitivity in detecting small bowel tumors, and CT enterog-

raphy with a sensitivity of 85-95% [20-22]. Evaluation of the small intestine on CT is best when the bowel is properly cleansed, adequate doses of intravenous contrast are used, multi-planar reconstructions are available, both arterial and venous phases are acquired to assess for tumor vascularity and washout, and oral contrast is administered to allow for both proper distention of all bowel loops and accurate delineation of the mucosa with appreciation of the pattern of mucosal enhancement [23]. While both positive and neutral oral contrast materials are used, neutral oral agents are sometimes preferred over positive barium contrast because the latter can obscure subtle hyperenhancement close to the lumen.

When creating a differential diagnosis of a detected small intestine mass on CT or MRI it is important to keep in mind certain characteristics which help to form an initial impression and determine the most likely origin of the tumor. These include location in the small intestine (jejunal or ileal, more proximal or distal), number of masses, exophytic or intramural growth, enhancement pattern and vascularity, tissue properties based on Hounsfield units in CT and signal intensity in various MRI sequences, calcifications, mesenteric involvement (masses, lymph nodes, stellate pattern), extra-intestinal involvement (known history of or imaging findings indicating primary tumor or evident hepatic and splenic findings) [19]. We will highlight how various small intestine tumors tend to present with respect to these characteristics. Finally, we will briefly discuss the imaging findings in AFH.

ADENOCARCINOMA

The majority of small bowel adenocarcinomas involve the duodenum, while the rest are mostly located in the proximal jejunum near the ligament of Treitz [25]. Appearance on CT varies, but in a typical scenario this tumor will present as a single local asymmetrical annular thickening of a short segment of bowel wall with elevated shoulder-like borders or a distinct exophytic mass; in both cases the lumen is asymmetrically narrowed, the tumor density is closest to soft tissue and enhancement is only moderate due to

hypovascularity [19, 26-28]. The tumor itself is rigid and therefore can cause intussusception or bowel obstruction [26]. Invasion into the mesentery or vessels and regional lymph node enlargement may be present, distant metastases may be noted [19]. Fluoroscopic imaging with barium contrast may reveal a typical "apple core" sign and mucosal ulceration [19, 28].

CARCINOID

In contrast to adenocarcinomas, carcinoid tumors are most common in the distal ileum, often within 60 cm of the ileocecal valve; recently an increasing number of carcinoids in the duodenum is observed [28]. These tumors are among the smallest to involve the GI tract, often just a few centimeters in size [28]. Typically on CT carcinoids are recognized as solitary or multiple, intramural or exophytic soft tissue masses with marked enhancement during the arterial phase due to hypervascularity (best seen with oral water contrast) and calcifications; most specific finding associated with carcinoid is a desmoplastic reaction of the mesentery due to local spread, which involves fat stranding, a visible stellate pattern and angulation or tethering of small bowel loops. Clinical and radiological signs of small bowel obstruction may be present, although less often than in adenocarcinomas, due to growth into the lumen and deformation of small bowel loops [19]. Often the primary tumor is hard to visualize and diagnosis is first suspected based on mesenteric involvement or hypervascular hepatic metastases [19, 26-28]. Suggestive clinical history of serotonin overproduction (flushing, diarrhea, palpitations) can guide the radiologist to look more closely for typical features of carcinoid with the tools of nuclear medicine (somatostatin receptor scintigraphy, I-131 labeled MIBG or whole-body F18 dopa PET) [19].

LYMPHOMA

This tumor affects the small bowel with no predilection to either proximal or distal parts, but it is more common in the stomach [26]. Lymphoma in the small bowel can be primary, limited to small bowel and mesentery, or second-

ary, with involvement of extraintestinal organs (liver, spleen) and other lymph nodes [19]. The key feature differentiating lymphoma from both adenocarcinomas and carcinoids is the absence of obstruction [19]. Several different patterns of presentation on CT are common in lymphoma: most common is a single infiltrating bulky circumferential thickening of a relatively large segment of small bowel wall with no obstruction due to the pliability of tumor tissue. Other presentations include multiple intramural or mesenteric masses, aneurysmal dilation due to replacement of smooth muscles with lymphoid tissue and damage to the myenteric plexus and exophytic, sometimes ulcerated mass (can be mistaken for adenocarcinoma or GIST) [19, 26-28]. Lymphomas as a rule are less enhancing than other gastrointestinal tumors, and if enhancement is present it is usually homogenous [28]. Characteristic sign of lymphomas is bulky retroperitoneal or mesenteric adenopathy. Due to markedly enlarged lymph nodes, subsequent surrounding of adjacent vessels can develop and so called "sandwich" sign can be observed after injection of IV contrast [19, 27].

METASTASIS

Radiological signs of metastases in part depend on their origin. Malignant melanoma metastases are single or multiple masses in the submucosa without small bowel obstruction, sometimes with aneurysmal dilation due to a similar mechanism as in lymphoma; "target" sign may be appreciated when a clearly demarcated mass enhances and protrudes into the lumen [19]. Metastases from breast and lung cancer are rigid soft tissue masses and can cause luminal narrowing and small bowel obstruction, often looking very similar to primary small bowel adenocarcinoma [19]. Metastases from intraperitoneal organs (primary gastrointestinal, ovarian tumors) tend to diffusely involve the bowel loops and adhere them together, show signs of mesenteric involvement and stellate pattern similar, but not identical to, the desmoplastic reaction of carcinoid tumors [19]. Thus, when a mass suggestive of primary adenocarcinoma, carcinoid tumor or

lymphoma is discovered, particular care must be taken to determine whether the mass is primary or secondary in origin with further imaging and other investigations.

GIST (FORMERLY LEIOMYOSARCOMA)

This tumor arises from the interstitial cells of Cajal and can involve the duodenum, jejunum or ileum, however the most common location is the stomach [19]. Typically it presents in patients over 50 years old [27]. GIST can be benign and malignant, but radiological appearance does not allow for precise differentiation between these possibilities [27]. It is noted however that malignant GIST is usually over 5 cm in size [19]. On CT examination the tumor is most often an exophytic relatively large soft tissue mass with a smooth outline, ulceration, and heterogenous, mostly peripheral, enhancement with central necrosis or cystic component [19, 26-28]. In some cases, aneurysmal dilation due to cavitation (not muscle or nerve damage like in lymphomas or metastases) [19], small hemorrhages and calcifications are evident [28]. Metastasis is mostly by direct invasion, but hematogenous spread to the liver is also typical with metastases being hypovascular or cystic in their appearance [26, 28].

LIPOMA

This common benign tumor is easily distinguished on CT by its characteristic fat density in appearance and Hounsfield units [19].

HEMANGIOMA

It is most common in the jejunum; due to its vascular nature hemangioma can present with almost insignificant or profuse gastrointestinal bleeding and/or corresponding anemia [29]. Hemangioma is usually small, often contains phleboliths [19]. On CT small bowel hemangiomas behave similarly to liver hemangiomas: there is a slow rim-like heterogenous peripheral contrast uptake in the early phases, progressing centrally and ending in complete or almost complete homogenous enhancement of the mass in later phases [30].

NEURAL TUMORS

Typically present as smooth or lobulated, well-defined masses; calcification is common in all types of neural tumors; additional lesions might suggest that the tumor is malignant, but no specific radiological findings exist for determining malignant potential [31].

HEREDITARY POLYPOSIS SYNDROMES

Small bowel is most often affected by Peutz-Jeghers syndrome, which presents with a large number of small filling defects on barium studies or discrete masses on CT. Typical mucocutaneous involvement (pigmentation) of the perioral area, palms and soles is seen clinically [19].

RADIOLOGICAL APPEARANCE OF ANGIOMATOID FIBROUS HISTIOCYTOMAS

CT findings are nonspecific, as it was in our case, and they may show only a heterogenous mass with both solid and cystic components and possibly some irregular enhancement [9]. To better visualize the tumor it is necessary to perform an MRI.

A recent study on MR imaging in AFH revealed several new findings characteristic of AFH: first, the lesions exhibited a "double-rim sign" on T2-weighed and contrast-enhanced images, which consisted of both a high and low signal intensity components (the outer component being of high signal intensity); second, there were marginal strings of infiltrative neoplastic tissue spreading into the surrounding fat and muscle [32].

AFH on MR usually has both cystic and solid components, contains fluid-fluid levels, is predominantly heterogenously hyperintense on T2-weighed images with some regions of local hypointensity, isointense or hypointense to muscle on T1-weighed images, may display surrounding edema, usually exhibits variable contrast enhancement or an enhancing pseudocapsule [9, 32-33]. Interestingly, authors of an article describing 7 AFH cases noted that all of those cases were initially misdiagnosed based on MRI, and erroneous diagnoses included hemangiomas, arteriovenous malformations, hematomas and sarcomas [33].

CONCLUSION

In this report we presented to our knowledge the first case of an angiomatoid fibrous histiocytoma of the adrenal gland which later metastasized to the jejunum. AFH presented with no specific clinical or radiological findings, therefore the diagnosis had to be confirmed by histological and immunohistochemical analysis after resection of the tumor.

Angiomatoid fibrous histiocytoma has several characteristic findings on MR imaging, including a double-rim sign, fluid-fluid levels, and marginal infiltrating strings of tumor tissue.

Tumors of small intestine are rare, and careful protocol selection is necessary to detect and classify the tumor. In order to distinguish between benign and malignant tumors of the small intestine it is crucial to evaluate the number, location, vascularity, calcifications, growth and enhancement patterns, mesenteric and extra-intestinal involvement of the tumors.

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