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ABSTRACT

Benign retroperitoneal tumors (BRT) represent a rare group of heterogeneous diseases. The literature lacks high-quality evidence about the optimal management of BRT, and most of the information available takes the form of case reports or case series. The aim of this review is to provide an overview of current management strategies for adult patients with BRT.

A literature search using PubMed indexed articles was conducted and BRT were classified into five different biological subgroups: 1) lipomatous tumors, 2) smooth muscle tumors, 3) peripheral nerve sheath tumors, 4) myofibroblastic tumors, and 5) others. Tumors that are primarily pelvic in origin were excluded.

Despite the significant heterogeneity of the disease, several generic considerations have emerged and can be applied to the management of BRT. Specifically, the risk of misdiagnosing a BRT with another pathology such as retroperitoneal sarcoma is notable. When encountered, suspected BRT should therefore be referred to a specialized sarcoma center. Multidisciplinary tumor boards, present at these centers, have a pivotal role in managing BRT. The decision of whether to offer surgery, nonsurgical treatment or a "watch-and-wait" approach should be made after multidisciplinary discussion, depending on tumor histology. Moving forward, collaborative research efforts dedicated to BRT remain crucial in gathering evidence and knowledge to further optimize patient care.

1. Introduction

In contrast to retroperitoneal sarcomas (RPS), which are relatively well described, the literature broadly lacks information about benign retroperitoneal tumors (BRT). They constitute a heterogenous group of diseases that represent a diagnostic and therapeutic challenge that can easily be misdiagnosed as RPS.

The aim of this review is to give an overview of the management of BRT in adults. Herein, we define BRT as "any solid or cystic lesion arising in the retroperitoneal space and with no or remote potential

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of metastatic spread." Our aim is to give emphasis on those tumors that can masquerade or mimic RPS. Included are benign lipomatous tumors, smooth muscle tumors, peripheral nerve sheath as well as fibroblastic tumors and among others. Included are also some locally aggressive tumors as inflammatory myofibroblastic tumors. Excluded are solid non-RPS tumors (e.g. lymphoma, neuroendocrine, adrenal). While some BRT types can occur in the pelvis or mesentery, our focus is in the retroperitoneum. We acknowledge that other benign entities could be found in the retroperitoneum; however, either because these are organ specific (e.g pancreatic pseudocyst) or non-tumorous (e.g. hematoma) our focus was limited on the above mentioned BRT.

2. Presentation and diagnosis

As BRT represent a heterogenous group of diseases, the exact incidence is difficult to quantitate. Nevertheless, in a study analyzing 314 patients who presented with a retroperitoneal mass and received a percutaneous biopsy, 21% were diagnosed with BRT in contrast to 54% who were diagnosed with RPS [1]. Among BRT, lipomatous tumors were the most common, affecting 34% of patients, followed by spindle cell neoplasms NOS and schwannoma, in 23% and 18% of patients, respectively.

The clinical presentation of BRT can be similar to that of RPS. Patients with BRT may be completely asymptomatic with their tumor discovered incidentally during imaging performed for other reasons; alternatively patients may have a palpable mass. The diagnosis of BRT may in some cases be made only after ruling out initially presumed RPS. As there can be overlap with RPS, when a retroperitoneal mass is discovered, the patient should be referred to a specialized sarcoma center, where an adequate percutaneous biopsy can be performed. The importance of performing a percutaneous biopsy and its accuracy as well as its safety have been documented [2,3]. It is in fact, recommended by current management guidelines for retroperitoneal sarcoma, to differentiate these benign diseases [4,5]. Within a multidisciplinary sarcoma tumor board, pathology and radiology data can be correlated and the next steps in management discussed among the clinicians. In the majority of cases, conservative management or active surveillance represent the most appropriate management options for BRT (Table 1).

3. Lipomatous tumors

The most common benign lipomatous tumors in the retroperitoneum include angiomyolipoma, myelolipoma, myolipoma, and lipoma. There are also cases reports of retroperitoneal hibernoma (notably active on PET) [6] and other benign processes such as encapsulated fat necrosis from pancreatitis or trauma [7]. The broad range of benign diagnostic possibilities and the overarching need to rule out liposarcoma highlights the importance of radiologist and pathologist expertise when evaluating a patient with a retroperitoneal lipomatous tumor.

3.1. Angiomyolipomas

Angiomyolipomas (AML) belong to a family of tumors known as perivascular endothelial cell tumors or PEComas. The vast majority of AML are thought to originate from the kidney and feature variable components of fat along with blood vessels and smooth muscle [8]. Up to 80% of AML occur sporadically, but the remaining 20% are associated with the autosomal dominant hereditary syndrome tuberous sclerosis (TS) and lymphangioleiomyomatosis (LAM) [9]. On cross sectional imaging, AML can have a "beak" or "claw sign" suggesting renal parenchymal involvement or presence of dysmorphic feeding vessels arising from the renal hilum, which help to distinguish AML from well-differentiated (WD) liposarcoma (Fig. 1). Importantly, AML lacks the calcification that can be seen in dedifferentiated (DD) liposarcoma or renal cell carcinoma. However, in cases of diagnostic uncertainty, a biopsy is recommended.

On histopathology, AML express immunohistochemical markers of smooth muscle (e.g., smooth muscle actin (SMA) and calponin) and melanocytic (e.g., HMB45, MelanA and MITF) differentiation. AML is negative for liposarcoma markers (e.g., MDM2, CDK4).

AML can be classified in two different subtypes: a classic type, which is completely benign, and an epithelioid type, which can potentially metastasize [10]. It is therefore essential to distinguish between the two, which can also be made on diagnostic imaging [11–13]. Classic AML have a fatty component that is characterized

Table 1
Characteristics of main benign retroperitoneal tumors.

	Subtypes				
	Lipomatous Tumor	**Benign Smooth Muscle Tumors**	**Benign Peripheral Nerve Sheath Tumors**	**Myofibroblastic Tumors**	**Other Benign Retroperitoneal Tumors**
Representative subtype	Angiomyolipoma	Leiomyoma	Schwannoma	Inflammatory myofibroblastic tumor	Ganglioneuroma
Differential Diagnosis	WDLPS	LMS	Neurofibroma	Other spindle cell lesions	Renal cell carcinoma, pheochromocytoma, other sarcomas
Most Common Clinical Presentation	Incidental finding	Incidental finding	Incidental finding/ neuropahtic pain	Incidental finding/ 30% presenting with pyrexia, fatigue, anemia	Incidental finding
Radiological Key Features	"Beak" or "claw" sign	None	High intensity lesion peripherally and low intensity lesion centrally at T-2 weighted MRI	None; variable	None
Pathological Key Features	Express immunohistochemical markers of both smooth muscle and melanocytic differentiation	Smooth muscle marker (desmin, SMA, h-caldesmon positive; often ER and PR positive; low mitotic activity	S100 protein and SOX10 positive	Myofibroblastic cells; ALK gene rearrangement	Ganglioneuroma: Nerve sheath-type spindle cell background with intermingled ganglion cells
Management	Conservative (for the classic type)	Conservative	Conservative	Surgery	Conservative

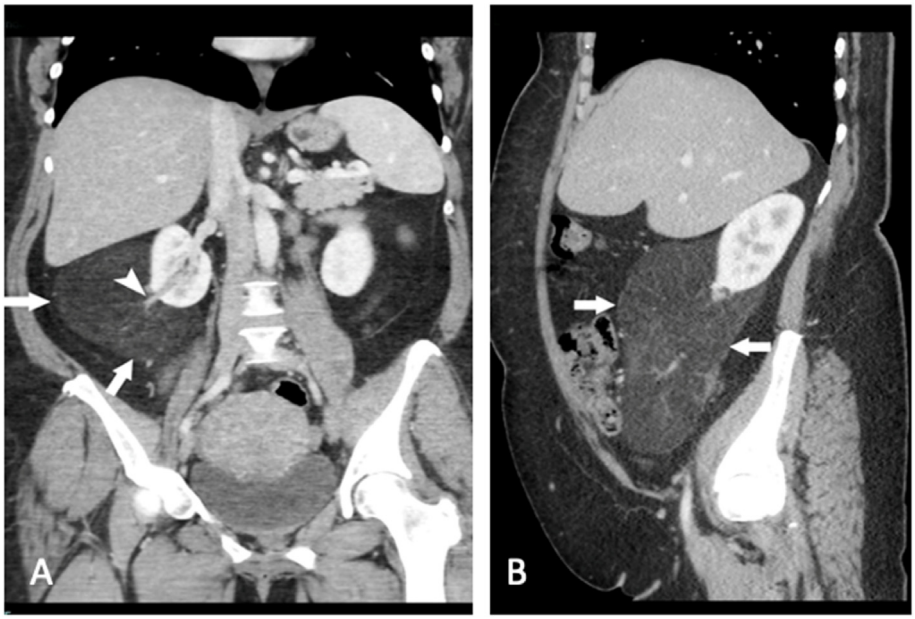

Fig. 1. Extrarenal angiomyolipoma: Coronal (A) and sagittal (B) images of contrast enhanced CT scan shows up to 18 cm mass (arrows) with mixed fatty and non-fatty elements partially draping around the anterolateral aspect of the right kidney. No internal calcification is seen. A prominent vessel is seen arising from the renal hilum (arrowhead). The mass was surgically excised and proven angiomyolipoma at pathology.

by negative density on CT-scan, whilst epithelioid AML contain a minimal amount of fat and can involve the renal vein [14]. In addition, epithelioid AML usually show heterogeneous enhancement on CT-scan.

The management of patients with AML depends on the suspicion of malignancy as well as tumor size and presence of symptoms. In a large series, Bhatt et al. found that over 90% of patients affected by AML did not have a significant increase in tumor size over time and no difference was found when AML larger and smaller than 4 cm were compared [15]. Therefore, for small, classic AML and in absence of symptoms, surveillance is usually recommended [16]. If surgery is performed, en bloc resection with partial as opposed to total nephrectomy is preferred, if technically feasible. It should be borne in mind that bleeding is a possible complication for large tumors, occurring in approximately 12% of patients, and selective embolization can be used as a valid treatment option [17]. For patients with TS, who can have bilateral AML, systemic therapy with mTOR inhibitors may be indicated [18].

3.2. Myelolipomas

Myelolipomas (MeL) are benign tumors that have juxtaposed mature fat and hematopoietic cells of all three hematopoietic cell lineages (Fig. 2 A). Although most commonly adrenal in origin, there are case reports of extra-adrenal MeL in the retroperitoneum and pelvic (pre-sacral) space [19,20]. These tumors appear to occur more commonly on the right, but otherwise there are no radiologic features that readily distinguish MeL from other retroperitoneal lipomatous tumors [7]. Despite the marrow component, on PET the FDG-avidity generally appears to be low but may vary depending on the degree of intratumoral hematopoiesis [21,22]. Definitive diagnosis is made by histopathology. Although MeL are most commonly nonfunctioning, in some patients, there can be aberrant hormone (e.g., glucocorticoid, catecholamine) production or hypertension, thought to be associated with mass effect on the ipsilateral adrenal gland [23,24]. In a large, single institution review of MeL, a third of patients presented with hypertension. However, in this study it was unclear if hypertension was due to confounding variables (e.g. obesity) as opposed to the MeL per se. Best-practice management of MeL is still unclear overall, and observation is likely appropriate for smaller, asymptomatic tumors. Similar to AML, however, larger MeL can present with rupture and hemorrhage requiring urgent intervention [25].

3.3. Myolipomas

Myolipomas (MyL) are another rare variant of lipomas which contain mature fat admixed with smooth muscle cells (Fig. 2 B). Interestingly, MyL appear to have a very strong female predilection and in the largest case series to date (n = 34), almost half occurred in the retroperitoneum [26]. There are no distinguishing radiologic features, and similar to liposarcoma, retroperitoneal MyL are frequently large in size [26,27]. On histopathology, in addition to smooth muscle markers (desmin, SMA), MyL very often express estrogen receptors (ER), and HMGA2 [26]. Immunohistochemical markers for WD/DD liposarcoma (MDM2, CDK4) and AML (HMB45) are negative. Severe symptoms or complications have not been reported and clinical outcomes appear to be excellent after surgery. However, due its rarity, the appropriate management including the role of observation is unknown. Presence of ER and progesterone receptors (PR) in MyL, also reported by others [28,29], suggests the possibility of drug inhibition as a potential therapeutic option.

3.4. Lipomas

Once liposarcoma, AML, MeL and MyL have been excluded, lipomas can be considered in the differential diagnosis (Fig. 2 C). The existence of retroperitoneal lipomas is debated, but these tumors certainly continue to be described in case reports [30–32]. Lipoma-like WD liposarcoma can mimic retroperitoneal lipoma as cellular atypia can be minimal or even absent (sometimes because of specimen sampling), but true retroperitoneal lipomas lack evidence of *MDM2* amplification with fluorescence *in situ* hybridization. To date, the largest series of pathologically stringent retroperitoneal lipomas includes 19 patients [33]. Only half of these patients had

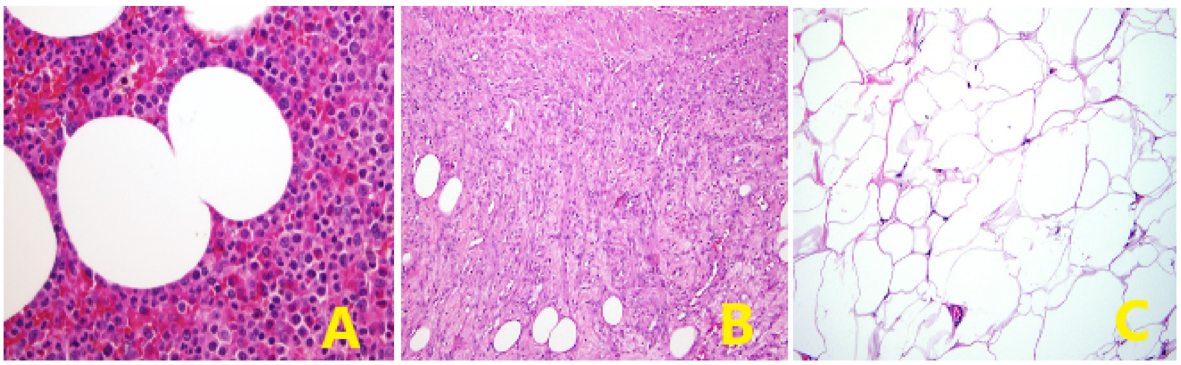

Fig. 2. Myelolipoma (A) This comprises sheets of mature adipocytes with variable amounts of hematopoietic cells, comprising all three hematopoietic lineages. Myolipoma (B) Mature fat, in this lesion present as clusters of mature adipocytes, is intermingled with bundles of bland smooth muscle cells lacking atypia or mitotic activity. Lipoma (C) True retroperitoneal lipomas are rare, and need to be distinguished from lipoma-like well-differentiated liposarcoma. This neoplasm is composed of sheets of mature adipocytes lacking any atypia. Fat necrosis is present. Other architectural features of well-differentiated liposarcoma, such as broad fibrous septation, are also lacking, and there was no evidence of MDM2 amplification with fluorescence *in situ* hybridization.

follow-up (median: 6 months) and although no recurrences were noted after surgery, recommendations for appropriate management remain unclear.

4. Benign smooth muscle tumors

4.1. Leiomyomas of deep tissue

4.1.1. Benign spindled leiomyomas of deep tissue

Leiomyomas of deep tissue (LDT), also known as leiomyomas beyond the uterus, are rare tumors that arise from smooth muscle cells. They usually occur within the genitourinary tract, but can arise very rarely within the retroperitoneum [34], mainly amongst perimenopausal women [35]. The clinical presentation is varied such that tumors may be recognized incidentally, synchronously at the time of detection of uterine leiomyoma, or can grow to large size to cause adjacent organ compression [36,37]. Their appearance on imaging is of a rounded circumscribed mass which may contain calcifications, and they cannot easily be distinguished from their malignant counterparts [35]. Therefore, these lesions typically require biopsy for diagnosis [36]. Surgery may be indicated in case of diagnostic uncertainty. LDT are similar to uterine leiomyomas on histology and immunohistochemistry (ER and PR positive), but mitotic activity is generally low and below 10 mitotic figures per high power fields [35]. Higher mitotic levels and cellular atypia would suggest metastatic uterine leiomyosarcoma, or rarely a primary ER positive leiomyosarcoma [38]. In addition, leiomyomas may be non-degenerated or degenerated, with their various forms including cystic, hemorrhagic, fatty, hyaline and myxoid [39]. Overall, treatment consists of conservative management. When resection is performed, recurrence is rare [40].

4.1.2. Extrauterine leiomyomas with unusual growth patterns

Benign metastasizing leiomyomas (BML) are characterized by solitary or multiple nodules of benign-appearing smooth muscle tumors. They are considered benign leiomyomas, and not as a variant or malignant myoma. They may present synchronously or metachronously to the primary uterine leiomyoma in premenopausal women, which may also act as a clue to their diagnosis [36,41,42]. Additional rare growth patterns include parasitic, disseminated peritoneal leiomyomatosis and intravenous leiomyomatosis [36]. While BML do have a predilection for the lungs, these lesions do occasionally arise in the retroperitoneum along with other sites [41]. Given their rarity and overall diagnostic challenge, a biopsy is useful and its outcome typically mimics that of uterine leiomyoma [38]. The absence of atypia, mitotic activity, necrosis and invasion aid in ruling out metastatic low-grade leiomyosarcoma, smooth muscle tumors of uncertain malignant potential (STUMP), lymphangioleiomyomatosis and leiomyomatous hamartoma [36]. Although no standardized treatment recommendations exist, therapeutic options include surveillance, hormonal therapy and surgery [36]. Hysterectomy is recommended when there is suspicion of underlying smooth muscle tumors of uncertain malignant potential [43].

4.1.3. Smooth muscle tumors of uncertain malignant potential

STUMP are considered a histologic intermediate and distinct from leiomyoma variants and leiomyosarcoma [44]. Similarly, these lesions present in premenopausal women in their 4th decade as an incidental finding or with compressive symptoms, and non-diagnostic imaging features some overlapping features of leiomyosarcoma [45–47]. STUMP lesions typically meet one of the three features of Bell's criteria for leiomyosarcoma, including coagulative tumor cell necrosis, cytological atypia, and increased mitotic activity [48]. The biologic behavior is variable, and these lesions can recur as either STUMP or leiomyosarcoma in 11–28% of patients [49,50]. Consequently, authors have supported close surveillance with cross-sectional imaging every 6 months for 5 years and annually thereafter [49]. Although no standardized treatment recommendations exist for STUMP located within the retroperitoneum, therapeutic options can be extrapolated from uterine STUMP, where resection and surveillance may be considered [47,49].

5. Benign peripheral nerve sheath tumors

In the retroperitoneum, benign peripheral nerve sheath tumors are mainly represented by schwannomas or, less often, neurofibromas.

5.1. Schwannomas

Schwannomas are benign lesions and typically present as a sporadic mass, although they can occasionally be associated with genetic syndromes such as type 2 neurofibromatosis or schwannomatosis (Fig. 3 A) [51]. Because schwannomas arise from the nerves, patients with these lesions can present with neuropathic pain or numbness. Schwannomas can occasionally occur as a cystic lesion (Fig. 4). Histologically, these are variably cellular tumors comprising areas of densely cellular spindle cells called Antoni A

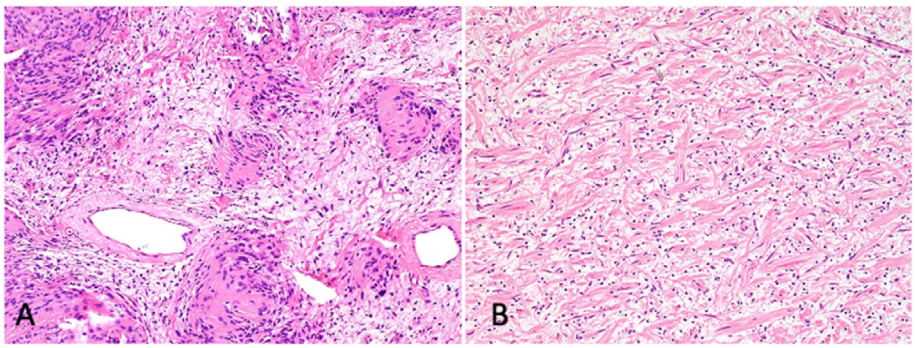

Fig. 3. Schwannoma (A). This example is variably cellular, with relatively cellular areas of spindle cells in palisaded distributions, with surrounding more sparsely cellular areas in which spindle cells are distributed within fibromyxoid stroma, with background vascularity. Examples that are more uniformly cellular can morphologically mimic smooth muscle tumors and gastrointestinal stromal tumor. Neurofibroma (B). This is composed of spindle Schwann cells showing elongated, slightly tapered or buckled nuclei, with collagen bundles, slender fibroblasts and scattered lymphocytes.

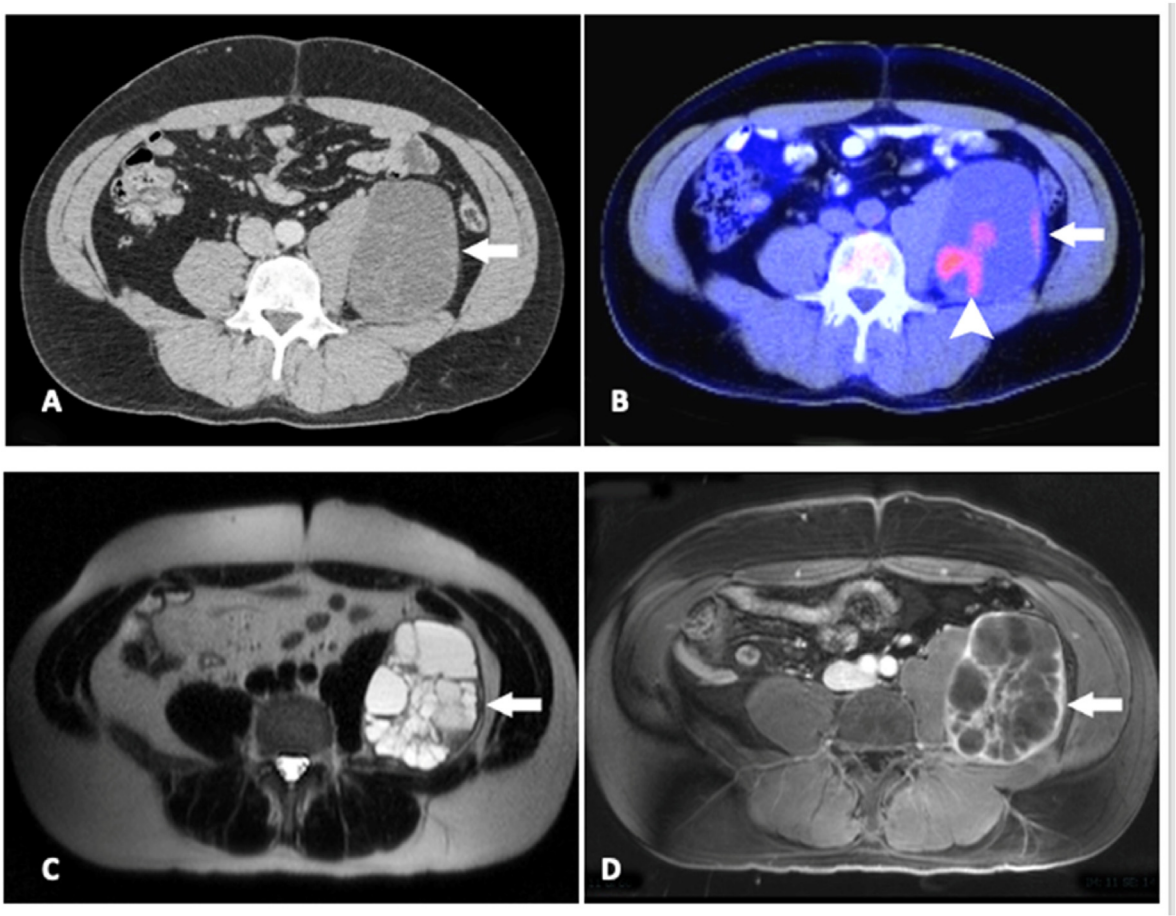

Fig. 4. Cystic schwannoma: Contrast enhanced CT scan of the abdomen (A) shows up to 9.9 cm predominantly cystic mass (arrows) with internal septations in the left retroperitoneum causing mass effect on the left psoas muscle. On fused PET-CT image (B) there is low level metabolic activity in most of the lesion, with focus of increased metabolic activity (arrowhead). On T2 HASTE MRI (C), the mass is predominantly hyperintense with septations that enhanced on post contrast T1 with fat saturation image (D). The mass was surgically excised and was pathologically proven to be schwannoma with cystic degeneration.

regions, and areas of less cellular, more myxoid matrix named as Antoni B. Nerve sheath differentiation is confirmed with positive immunohistochemistry for SOX10 and S100 protein. Radiologically, MRI scans can facilitate the diagnosis; usually, schwannomas appear as a high intensity lesion peripherally and low intensity centrally at T2-weighted images. The most comprehensive study to date is a retrospective cohort series involving 12 different global institutions from the Transatlantic Australasian Retroperitoneal Sarcoma working group (TARPSWG) [52]. In this study, 485 patients with retroperitoneal or pelvic schwannomas were analyzed, with 61% receiving surgery. The most common reason for surgical intervention was the presence of a symptomatic lesion, whereas the decision not to operate was chiefly based on the lesion proving asymptomatic or stable during the follow-up, or presenting as an asymptomatic lesion with an operation carrying a risk of major nerve injury. Malignant transformation was not observed in any of the patients kept under surveillance. Major postoperative complications (Clavien-Dindo grade 3) occurred in 8.5% of those who

underwent surgery. Approximately 97% of patients received an R0/1 resection with a relatively low recurrence rate of 6.7%. For those who received an R2 resection, no significant tumor growth was detected during follow-up. The authors suggested that symptoms on presentation and existing evidence of rapid expansion were the primary indications for surgery. If schwannomas are detected as an incidental finding, a biopsy should be followed by surveillance imaging to predict tumor growth characteristics, and surgery should be considered on an individual basis. In the majority of cases, conservative management is the preferred option.

5.2. Neurofibromas

Neurofibromas represent the most common type of peripheral nerve sheath tumor, but their presentation in the retroperitoneum is rare (Fig. 3 B). Therefore, evidence about this pathology limited and is mainly represented by case series or case reports [53,54]. Neurofibromas can occur as sporadic or plexiform lesions. The former is pathognomonic for type 1 neurofibromatosis and there is a risk of transformation into malignant peripheral nerve sheath tumors (MPNST). When malignant transformation is suspected, FDG-PET is a useful and sensitive test to distinguish between neurofibromas and MPNST [55]. Surgery should be considered if a malignant transformation is suspected.

6. Myofibroblastic tumors

6.1. Inflammatory myofibroblastic tumors

In contrast to the other purely benign tumors discussed in this review, inflammatory myofibroblastic tumors (IMTs) are classified as mesenchymal neoplasms of intermediate (rarely metastasizing) biologic potential and with locally aggressive features (Fig. 5 A). In fact, they are characterized by a propensity to local invasiveness as well as the remote possibility of distant metastases, reported in less than 5% of cases [56]. IMTs can present throughout the body, with approximately two-thirds presenting in the retroperitoneum and abdominal cavity [57]. At this body location, IMTs may on rare occasions be multifocal at presentation. Approximately 30% of patients present with associated constitutional symptoms characteristic of generalized inflammation, such as pyrexia, weight loss, fatigue, anemia and raised platelets [57]. These symptoms often resolve when the tumor is removed. Recurrence of constitutional symptoms may be a harbinger of recurrent disease.

Radiological features vary from an ill-defined, infiltrating lesion to a well-circumscribed soft-tissue mass [58]. Histologically, IMTs are composed of myofibroblastic and fibroblastic cells with variable architecture, with prominent intermingled chronic inflammatory infiltrate, typically of lymphocytes, plasma cells and sometimes eosinophils. At least 50% of tumors harbor anaplastic lymphoma kinase (*ALK*) gene rearrangements on chromosome 2p23, which leads to constitutive tyrosine kinase activation [56,57,59]. Evaluation of the ALK status is clinically relevant for patient prognosis, as ALK-negative IMTs tend to have a more aggressive clinical course, as well as from a therapeutic perspective [56–62].

Surgery should be offered to patients diagnosed with IMTs. For retroperitoneal IMTs, cases that are locally advanced may benefit from neoadjuvant therapy with systemic anti-cancer agents or ALK inhibitors such as crizotinib. Most patients will have long-term benefit from surgery, with a 5-year overall survival rate of 98% [63]. However, local recurrence does occur at a rate of approximately 30% [56,57]. It is important to note that cases of spontaneous regression have been reported, albeit infrequently, with regression also reported in patients whose tumors have not been fully resected [64].

6.2. Retroperitoneal Desmoid-Type Fibromatosis

Desmoid-Type Fibromatosis (DTF) represents a rare myofibroblastic tumor (Fig. 5 B) [65]. In 90% of cases DTF is sporadic and characterized by the presence of a mutation in *CTNNB1* gene, whilst in the remainder it is associated with familial adenomatous polyposis (FAP) [65]. Intrabdominal (mesenteric or retroperitoneal) DTF is rare in the sporadic setting, but can reach up to 80% of cases when associated with FAP [66,67].

On cross-sectional imaging, DTF usually present as solid masses with ill- or well-defined margins, but cystic changes can be seen, and rare cystic mass with thick wall has been reported [68,69].

Diagnosis should be confirmed by core needle biopsy, with appropriate molecular testing for mutations in *CTNNB1*, which encodes β-catenin, or in the gene *APC* for patients without *CTNNB1* mutations or in the presence of a suspicion of familial adenomatous polyposis syndrome [70–72].

In general, the management of RP DTF should be consistent with recommendations for the management of DTF at other sites [70–72]. For asymptomatic patients, active surveillance with interval MRI or CT scan is recommended for 1–2 years and represents the first line approach to DTF regardless of their sites. The rationale for using this approach is to avoid overtreatment for patients who may regress spontaneously. In addition, it should be taken into account that although DTF can be locally aggressive, it does not have metastatic potential. If disease progression occurs (e.g. growth on 2 consecutive scans), the management should shift towards active treatment. In contrast to historic recommendations, the first

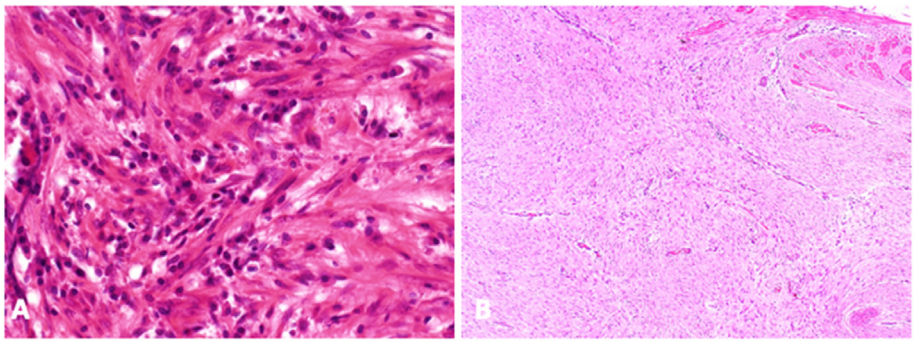

Fig. 5. Inflammatory myofibroblastic tumor (A): This example is composed of loose fascicles of spindle fibroblasts and myofibroblasts, with an intermingled moderate chronic inflammatory infiltrate, predominantly of lymphocytes and plasma cells. Desmoid-type fibromatosis (B): This tumor is composed of delicate, sweeping fascicles of bland, uniform spindle myofibroblasts with small vesicular nuclei and fibrillary cytoplasm, in collagenous stroma, with prominent background vascularity. There is infiltration of the surrounding local muscular structures (top right).

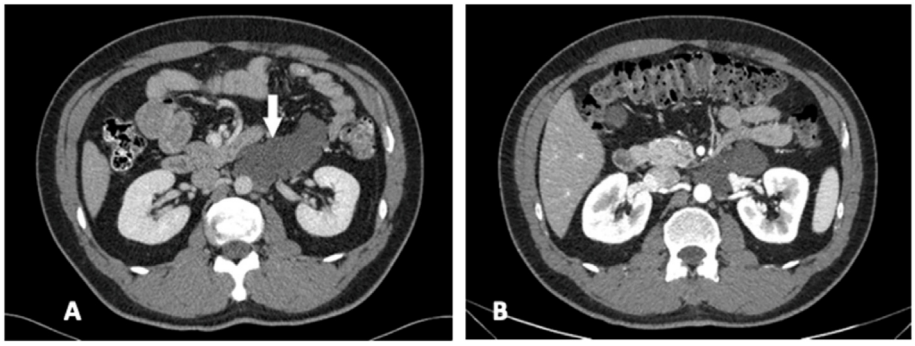

Fig. 6. Lymphangioma. Incidentally detected cystic mass on CT scan performed for abdominal pain. The mass has fluid attenuation and insinuates between the adjacent structures without causing mass effect (A). This was presumed lymphangioma and as the mass is asymptomatic, no intervention was done. Four and half years later, the mass decreased in size (B).

active treatment option for intrabdominal/retroperitoneal DTF is systemic therapy [71] and surgery should only be considered in case of failure of medical treatment.

7. Other benign retroperitoneal tumors

7.1. Ganglioneuromas

Ganglioneuromas are rare tumors that originate from neural crest cells along the sympathetic chain and within the adrenal glands. Arising *de novo* as primary lesions or from differentiation of immature neoplasms, ganglioneuromas are benign and the most mature of neurogenic tumors that include ganglioneuroblastomas and neuroblastomas [73].

Ganglioneuromas develop in patients of all ages and in both males and females at similar rates. Up to 52% of ganglioneuromas arise in the retroperitoneum [74]. Clinically, ganglioneuromas are frequently found incidentally on imaging or present with non-specific symptoms due to mass effect. Tumors develop most often sporadically and occasionally in the setting of hereditary syndromes, including Multiple Endocrine Neoplasia Type 2A, Multiple Endocrine Neoplasia 2B, Neurofibromatosis type-1, and Turner's Syndrome [75–78]. They have indolent disease courses and are usually hormonally silent, although there have been reports of tumors secreting catecholamines, cortisol, testosterone, and vasoactive intestinal peptides [79–82].

Diagnosis of ganglioneuromas can be difficult with implications for over- or under-treatment. These tumors have no specific clinical signs, symptoms, and laboratory findings. The lack of pathognomonic radiological findings for ganglioneuromas may lead to misdiagnoses for more aggressive tumors that share similar imaging characteristics, such as in the case of adrenal ganglioneuromas with renal cell carcinoma, adrenocortical carcinoma, pheochromocytoma, and sarcomas. Thus, pathologic diagnosis through biopsy and surgery provides more reliable diagnosis [83].

Historically, if safe and technically feasible, operative management with R0/R1 resection was been considered the mainstay therapy for ganglioneuromas, particularly those that are symptomatic, locally displacing, large, rapidly growing, or of uncertain biology. Operative intervention was pursued in nearly all patients in several single-institution case series [73,82–85]. Prognosis is usually favorable with rare instances of recurrence, as well as tumor progression in incompletely resected lesions [84,85]. In support of this, a recent TARPSWG's study analyzing 328 patients with ganglioneuromas has shown a recurrence rate of 1.4% in the retroperitoneum [86]. In contrast, non-operative management with active surveillance may be warranted, particularly for those with indolent biology or in cases in which the risks of surgical resection outweighing benefits. In fact, in the TARPSWG study, the majority of non-resected ganglioneuromas remained stable in size while only 7.8% of lesions displayed growth that later stabilized [86]. In the light of this, conservative management should be the preferred treatment moving forward.

The evolution of an immature neuroblastoma to a ganglioneuroma has been well-established, but the dedifferentiation of a ganglioneuroma into a neuroblastoma is rarely observed. A report by Kulkarni et al. described a spinal neuroblastoma that developed 11 years after resection of a retroperitoneal ganglioneuroma [87]. In the TARPSWG study, there were two retroperitoneal ganglioneuromas with transformation to neuroblastoma (0.6% of all cases) [86]. Suspicion or proven malignant degeneration warrants resection.

7.2. Retroperitoneal cystic lesions

Retroperitoneal benign cystic lesions comprise an extremely heterogeneous group of lesions. However, the widespread use of CT and MRI imaging for evaluating abdominal diseases and symptoms has increased the detection rate for retroperitoneal cystic lesions. For the purposes of this review, we focus our discussion on cystic lymphangiomas and mucinous cystadenomas. Other considerations in the differential diagnosis for cystic lesions include teratomas, epidermoid cysts and cystic mesothelioma.

7.2.1. Retroperitoneal cystic lymphangiomas

Cystic lymphangiomas are rare, benign malformations of the lymphatic vessels that are often seen in the pediatric population. Most cystic lymphangiomas occur in the head or neck, with only 5% occurring elsewhere. These masses can develop in the mesentery or retroperitoneum, where they can be locally invasive, involving surrounding organs and structures. Retroperitoneal cystic lymphangiomas in adults are very uncommon. On a CT-scan, cystic lymphangioma appears as a large, non-enhancing, thin-walled, and multiseptated cystic mass (Fig. 6) [88].

While surgical removal [89] is considered the gold standard for symptomatic cystic lymphangiomas, percutaneous or endoscopic aspiration may also be considered, especially in the case of involvement of other organs, although this is associated with a higher chance of recurrence [90].

7.2.2. Mucinous cystadenoma

Primary retroperitoneal mucinous cystadenomas are rare lesions that typically occur in women [91]. These lesions are similar in macro- and microscopic appearance to ovarian cystadenomas. They usually manifest as homogeneous, unilocular cystic masses at

the CT scan. Differentiation from other cystic masses is difficult on the basis of imaging, and cytology of aspirated fluid frequently fails to reveal the diagnosis since epithelial cells of the cyst wall may not have been aspirated. Therefore, complete surgical excision of the cyst is usually indicated for both diagnosis and treatment, especially if differential diagnosis with mucinous cystadenocarcinoma is uncertain [92,93].

8. Conclusions

Given their heterogeneity, BRT should not be considered as a single entity. It is evident that BRT can pose both diagnostic and therapeutic challenges. Specifically, the ability to distinguish between a benign lesion and a RPS should not be taken for granted. Establishing the diagnosis upfront is critical and as such, we recommend referral to sarcoma specialist centers, liberal use of biopsy and close discussion with radiologists and pathologists. While conservative management or active surveillance can be definitive treatment in the majority of BRT, in some types, surgery may be required. This review also highlights that further collaborative studies are required to better understand the behavior of these diseases and to optimize patient care.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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