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REVIEW ARTICLE

Hamartomas from head to toe: an imaging overview

¹FRANCISCA LEITER HERRÁN, MD, ²CARLOS S RESTREPO, MD, ³DANIEL I ALVAREZ GÓMEZ, MD, ⁴THOMAS SUBY-LONG, MD, ⁵DANIEL OCAZONEZ, MD and ⁴DANIEL VARGAS, MD

¹Departamento de Morfología, Universidad de Los Andes, Santiago, Chile

²University of Texas Health Science center at San Antonio, TX, USA

³School of Medicine, Universidad de Los Andes, Santiago, Chile

⁴University of Colorado-Anschutz Medical Campus, Aurora, CO, USA

⁵University of Texas Health Science Center at Houston, TX, USA

Address correspondence to: Dr Daniel Vargas

E-mail: daniel.vargas@ucdenver.edu

ABSTRACT

Hamartomas are tumours composed of mesenchymal tissues such as cartilage, fat, connective tissue and smooth muscle and can be found in virtually any organ system. These masses commonly develop sporadically, but are also seen in certain syndromes such as tuberous sclerosis or Carney triad. While their imaging appearance varies depending on the organ they arise from, findings are usually unique and a diagnosis can be confidently made. Radiologists must be aware of the clinical and imaging presentations of these lesions with the particular goal of avoiding unnecessary studies or invasive procedures. Furthermore, knowledge of common syndromic entities is crucial, as the radiologist may be the first to suggest the diagnosis.

INTRODUCTION

A hamartoma is a focal proliferation of cells and tissues typically found in the organ from which they arise. In spite of being characterized by the presence of mature elements, the architecture of the organ is not preserved. Eugen Albrecht is credited with first using the term hamartoma in 1904. The word hamartoma is derived from the Greek *to err*. Albrecht described hamartomas as tumour-like formations in which there is an abnormal mixture of normal components of the organ in which they occur either by amount, structure and degree of maturity or all three together.^{1,2} The line of demarcation between hamartomas and benign neoplasms is often unclear, since both lesions can be clonal. A hamartoma, however, contrary to a neoplasm, shows a self-limited growth.³ Hamartomas are composed of a mix of mesenchymal tissues and can be classified into different types according to the predominant tissue composing them: bone-forming, cartilage-forming, fibre-forming and non-matrix-forming hamartomas. They can arise in virtually all organ systems, either sporadically or in association with syndromic entities, some of which have a well-known genetic basis.

Imaging diagnosis is a key element in the characterization and management of these lesions. It is important to be familiar with the imaging spectrum of hamartomas and their syndromic associations, to avoid unnecessary and

potentially morbid treatment and follow-up. Despite the fact that the pathological basis of hamartomas and neoplasms is intrinsically different, cases of sarcomatous degeneration have been known to occur in specific situations, such as degeneration of an osteochondroma into a chondrosarcoma or development of neurofibrosarcomas in patients with Type I neurofibromatosis (von Recklinghausen disease). Therefore, knowledge of the clinical and imaging features of these lesions and syndromes is of utmost importance to the radiologist.

The aim of this article was to provide a description of the clinical features and imaging presentations of hamartomas occurring in different organ systems and to describe some of the main syndromic entities associated with the development of hamartomas.

SYSTEM-BY-SYSTEM REVIEW

Central nervous system hamartomas

Hypothalamic hamartomas

Hypothalamic hamartomas are developmental malformations consisting of tumour-like masses containing heterotopic neurons and glia, located in the tuber cinereum of the hypothalamus. These non-neoplastic masses predominantly affect patients who are male in the first or second decades of life and manifest clinically as central precocious puberty or episodes of gelastic seizures.⁴

These lesions can be classified into two subtypes depending on their anatomical location and clinical manifestations.⁴ Parahypothalamic hamartomas are pedunculated masses, commonly associated with precocious puberty.⁵ Intrahypothalamic hamartomas are sessile masses that lie within the substance of the hypothalamus, distorting the contour of the third ventricle. They are more frequently related to gelastic seizures than to precocious puberty.^{5,6}

At CT, these lesions are non-enhancing and isodense to grey matter. Over time, they demonstrate stability and lack of invasiveness. The presence of fat, haemorrhage and calcification has been reported, but only very rarely.⁷

At MRI, they are well-defined pedunculated or sessile lesions located between the infundibulum and mammillary bodies. These lesions appear homogeneous and demonstrate isointense and isointense to hyperintense signals on T_1 and T_2 weighted sequences, respectively. These lesions do not enhance after administration of contrast and show no elements of calcification (Figure 1).^{4,5} The absence of changes in morphology or signal intensity over time strongly supports the diagnosis of hypothalamic hamartoma.⁴ The differential diagnosis depends on the patient age and imaging characteristics at presentation.⁴ In paediatric patients, chiasmatic gliomas can have a similar imaging appearance, but in most cases are associated with enlargement of the optic chiasm, nerves or tracts. Hypothalamic gliomas can also arise in the tuber cinereum, but usually demonstrate variable degrees of cystic degeneration and calcification, which are rarely seen in hamartomas.⁷ Craniopharyngiomas can invade the floor of the hypothalamus and tuber cinereum, but in most cases are clearly centred in the suprasellar cistern. Also, they tend to show cystic degeneration and calcification.^{7,8}

Figure 1. Tuber cinereum hamartoma: an axial T_2 weighted MR image of the brain is showing an isointense mass (arrow) posterior to the pituitary stalk compatible with a tuber cinereum hamartoma.

Cortical tubers

Cortical tubers are congenital abnormalities consisting of focal cortical dysplasia secondary to an arrest in neuronal migration during fetal development. There is neuronal dysmorphism and the presence of large astrocytes. The normal architecture of the cortex is lost. Cortical tubers are present in about 90% of patients with tuberous sclerosis (TS) and are associated with intractable epilepsy and learning difficulties.⁹

The typical CT appearance of a cortical tuber is that of a cortically based hypoattenuating lesion, which may or may not expand the gyri. Non-enhanced studies are useful in demonstrating calcium, present in 50% of cases. These lesions may enhance.¹⁰

At MRI, they can present as subcortical nodules of varying signal intensities, depending upon the stage of myelin maturation and degree of calcification. Usually, cortical tubers have an increased signal intensity on T_2 weighted images (Figure 2) and decreased signal intensity on T_1 weighted images. Only 10% of cortical tubers enhance.¹¹ In neonates and infants, the signal intensity on T_2 weighted images is similar to that of an incompletely myelinated brain, making detection difficult. In this age group, the lesions are often more conspicuous on T_1 weighted images. While cortical tubers may be seen anywhere in the parenchyma, approximately 50% are seen in the frontal lobe.⁹ Differential diagnosis of cortical tubers includes grey matter heterotopias as well as sequelae of TORCH infections,

Figure 2. Cortical tubers in a 28-year-old male with tuberous sclerosis: an axial fluid-attenuated inversion-recovery MR image of the brain is demonstrating multiple areas of hyperintense signal with associated gyral expansion in the bilateral frontal and parietal lobes (arrows).

particularly cytomegalovirus, which often presents with diffuse calcification.

Subependymal nodules

Subependymal nodules represent hamartomatous changes in the subependymal tissue along the walls of the lateral and third ventricles. Subependymal nodules are seen in approximately 80% of patients with TSC and are often detected prenatally or shortly after birth.⁹ The imaging appearance of these lesions on CT and MRI evolves with the age of the patient. In the paediatric population, subependymal nodules are rarely calcified and thus may be difficult to detect on CT. In adults, the classic CT appearance of subependymal nodules is that of multiple small, densely calcified foci along the walls of the lateral ventricles.¹¹ At MRI, their appearance varies as the signal of the surrounding white matter and the amount of calcium changes. In infants, subependymal hamartomas are relatively hyperintense on T_1 weighted images and hypointense on T_2 weighted images. In adult patients, they are isointense on T_1 weighted images and hypointense on T_2 weighted images (Figure 3) and demonstrate variable degrees of enhancement with gadolinium. A large lesion size, location near the foramina of Monro and intense contrast enhancement should raise concern for subependymal giant-cell astrocytoma.¹²

Figure 3. Multiple subependymal nodules in a patient with tuberous sclerosis: an axial T_2 weighted MR image of the brain at the level of the lateral ventricles is showing multiple isointense to hypointense subependymal nodules bilaterally (arrows). The hypointense signal is in keeping with calcification.

Cerebellar hamartoma (Lhermitte-Duclos disease or dysplastic cerebellar gangliocytoma)

Cerebellar hamartoma (Lhermitte-Duclos disease or dysplastic cerebellar gangliocytoma) is a rare condition characterized by distortion of the normal cerebellar laminar cytoarchitecture. Most cases occur in adults, usually in the third and fourth decades, with no gender predilection.¹³ Pathogenesis remains uncertain: there may be a hamartomatous, neoplastic or congenital origin. However, association with Cowden syndrome suggests that it could fit the hamartoma-neoplasia spectrum of disease.^{13,14} Patients may be asymptomatic or present with symptoms secondary to mass effect, such as headache, ataxia, cranial nerve palsy, vertigo or cognitive impairment.¹⁵

CT demonstrates a non-calcified hypoattenuating cerebellar mass, with no significant enhancement. Occasionally, the mass may show mixed attenuation with scattered calcification. On MR, findings include a non-enhancing mass involving one cerebellar hemisphere. The left cerebellar hemisphere is more commonly involved. There is a characteristic tigroid pattern with hypointense signal on T_1 weighted images and hyperintense signal on T_2 weighted images (Figure 4). Hydrocephalus or syrinx may develop owing to mass effect on the fourth ventricle.^{13,15}

Figure 4. Cerebellar hamartoma (Lhermitte-Duclos disease): the axial T_2 weighted MR of the brain at the level of the cerebellum is demonstrating a large, hyperintense, intra-axial mass replacing most of the right cerebellar hemisphere (asterisk), causing a moderate mass effect over the fourth ventricle and pons. The thickened gyri and bizarre "gyriform" appearance can be noted.

These imaging features correlate closely with gross pathologic and histologic findings of abnormally thickened cerebellar folia owing to enlargement of the cortical cells and dysplasia of the sulci.^{13,15} Differential diagnosis for this entity is broad and should include subacute stage cerebellar infarction, cerebellar dysplasias and inflammatory processes (cerebellitis).

Head and neck hamartomas

Nasal chondromesenchymal hamartoma

Nasal chondromesenchymal hamartoma (NCMH) is a rare benign sinonasal hamartoma that predominantly affects infants younger than 1 year of age. The pathogenesis of NCMH remains unknown, but reports of occurrence in adolescents and adults support an underlying genetic predisposition in combination with possible environmental factors such as chronic inflammation and hormone stimulation.¹⁶

Clinical manifestations depend on the size and location of the lesion and include nasal obstruction, respiratory and feeding difficulties, rhinorrhoea and epistaxis. Orbital extension of the tumour can manifest as proptosis, enophthalmos, strabismus or impaired eye movement. Intracranial extension can result in neurologic manifestations such as hydrocephalus and oculomotor disturbances.¹⁷ A systematic review by Mason *et al*¹⁸ included 33 case reports of NCMH, 9 of which presented with intracranial extension and 15 of which presented with orbital extension.

Imaging studies are useful for assessing the extent of the lesion and involvement of adjacent structures.^{16,17} NCMHs are encapsulated masses with poorly defined margins. They are usually unilateral and often present with solid and cystic components.¹⁷ Calcification is a common finding and has been reported in about 45–50% of the cases on CT (Figure 5a).^{17,19} NCMHs have variable enhancement patterns on MRI. Owing to their cystic nature, NCMHs are usually isointense and hyperintense on T_1

and T_2 weighted images, respectively (Figure 5b).¹⁹ Radiological features that suggest an aggressive behaviour are erosion of the surrounding bone, cortical thinning, displacement and intracranial extension through the cribriform plate.^{16,17} However, no evidence has been found that these tumours may show malignant degeneration.²⁰

The differential diagnosis for a sinonasal mass in paediatric patients is broad and includes haemangioma, juvenile angiofibroma, inverted papilloma and ossifying fibroma, among others.²⁰

NCMH is managed surgically. Recurrence is unusual and is often the result of incomplete resection or microscopic seeding during surgery.¹⁹

Cardiothoracic hamartomas

Pulmonary hamartoma

Pulmonary hamartoma is the most common benign primary lung neoplasm and accounts for approximately 6–8% of solitary pulmonary nodules.²¹ Most of these lesions are found incidentally. Incidence is highest between the fourth and seventh decades of life, with male predilection (2:1 to 3:1).²² The precise aetiology of this lesion is unknown; however, evidence points towards genetic dysregulation, specifically a recombination of chromosomal bands.²³ Pulmonary hamartomas may be composed of tissues occurring normally in the lung: adipose tissue, epithelium, fibrous tissue and cartilaginous tissue. In up to 80% of cases, a predominant chondroid component is present. However, the presence of fat is the imaging hallmark of this lesion.²⁴

Typical CT findings consist of a solitary, well-defined, smooth, round or lobulated nodule or mass. 90% of pulmonary hamartomas and <10% are central or endobronchial. Fat is recognized on CT in about 60% of cases and may show a focal or diffuse distribution within the nodule. Popcorn-like

Figure 5. Nasal chondromesenchymal hamartoma: an axial CT image (a) is showing a mildly lobulated, partially calcified soft-tissue mass (arrow) within the right nasal cavity, producing a mass effect and bony remodelling without frank bone destruction. A coronal T_2 weighted (b) MR image is showing a heterogeneous, slightly hyperintense mass (arrow).

calcifications or central calcifications are present in about 5–50% of the cases (Figure 6). The differential diagnosis includes primary lung cancer, bronchogenic carcinoid and metastatic disease.^{21,24–26}

At fludeoxyglucose positron emission tomography, most pulmonary hamartomas show no or very mild metabolic activity. In some cases, however, they can demonstrate active metabolism, which can raise the suspicion for malignancy, especially when dealing with lipid-poor pulmonary hamartomas.^{27–29}

Multifocal micronodular pneumocyte hyperplasia

Multifocal micronodular pneumocyte hyperplasia (MMPH) is the second most common pulmonary manifestation in patients with TSC and is characterized by multifocal nodular proliferation of Type II pneumocytes along the alveolar septa.³⁰ The prevalence of MMPH in patients with TSC is similar in males and females (59% and 57%, respectively).³¹ MMPH may also be seen in females with sporadic lymphangioleiomyomatosis (LAM).³⁰ It is a non-progressive and asymptomatic condition. On CT, MMPH is characterized by multiple discrete, well-demarcated solid or ground-glass nodules, varying between 2 mm and 10 mm in size (Figure 7). In most patients, the nodules are distributed randomly and diffusely throughout the lungs. Upon follow-up, MMPH nodules are stable. Differential diagnosis is broad and includes miliary diseases, metastases and atypical adenomatous hyperplasia. While MMPH is most likely the cause of multifocal nodules in patients with TSC, follow-up is recommended.³¹

Cardiac rhabdomyomas

Cardiac rhabdomyomas are benign myocardial hamartomas and represent the most common primary cardiac tumour in infants and children. Most are diagnosed before the first year of life and >50% are associated with TSC. The majority of patients are asymptomatic and these lesions usually show spontaneous regression before the age of 4 years. Surgical resection is reserved

for cases of cardiac failure owing to left ventricular outflow tract obstruction or arrhythmias.³² Some cases may be detected *in utero*, especially those associated with fetal hydrops and death. Clinical features can include tachyarrhythmia, murmurs and heart failure. Most cases show spontaneous regression.³²

Rhabdomyomas typically originate within the ventricular myocardium or interventricular septum and are multiple in up to 60% of cases.³³ At MRI, they appear as isointense to normal myocardium on T_1 weighted images and mildly hyperintense on T_2 weighted images (Figure 8). Enhancement with gadolinium is less than that of myocardium on first-pass perfusion images, making them hypointense relative to myocardium. On late-phase images, enhancement equals that of myocardium.³⁴ The differential diagnosis for this lesion includes atrial myxoma, cardiac teratoma and fibroma.³⁵ Myxomas are usually intracavitary and most frequently seen in the left atrium, in most cases with an attachment near the fossa ovalis of the interatrial septum.^{32,34} Teratomas are heterogeneous extracardiac masses, usually multilocular with cystic and solid components. Intramyocardial teratomas have been reported, but are very rare.³⁶ Common locations include the pericardium, with an attachment close to the aortic root and origin of the pulmonary trunk.³⁴ Fibromas have intrinsic low T_1 and T_2 signals owing to their histological composition. On perfusion images, they show very late enhancement with varying patterns.³⁷

Breast hamartomas

Fibroadenolipomas

Fibroadenolipomas are uncommon tumour-like lesions composed of fibrous, glandular and adipose tissues, surrounded by a thin capsule of connective tissue. They most commonly affect females over 35 years.³⁸

On mammography, fibroadenolipomas appear as a well-demarcated mass with both fatty and soft-tissue contents surrounded by a thin radiodense capsule. They displace or overlap the adjacent normal breast tissue, resulting in the classic “breast within a breast” appearance (Figure 9). Coarse dystrophic or punctate calcifications can be seen. The sonographic appearance

Figure 6. Pulmonary hamartoma: a contrast-enhanced CT image through the lower lobes is showing a large, lobulated soft-tissue density mass in the left lower lobe with foci of low attenuation and calcification.

Figure 7. Multifocal micronodular pneumocyte hyperplasia in a patient with tuberous sclerosis: CT of the chest on lung window is showing multiple subcentimetre nodules (arrows).

Figure 8. Cardiac rhabdomyoma: a T_2 weighted dark-blood axial MR image through the heart is shows a large well-defined mass arising off the anterolateral wall of the left ventricle (arrow). The mass is appearing slightly hyperintense with respect to the myocardium.

of this lesion has wide variability owing to varying amounts of fatty, fibrous and glandular tissues.³⁹ The most common ultrasound appearance is that of a circumscribed and compressible oval mass, composed predominantly of a hyperechoic fatty component. Heterogeneous echogenicity is frequently present. In most cases, a hyperechoic halo can be seen, representing the compressed breast and fatty tissue.^{38,40}

At MRI, breast hamartomas are characterized by the presence of a fat signal, heterogeneous enhancement and the presence of a smooth hypointense rim, representing the surrounding capsule.⁴¹

Hepatic hamartomas

Hepatic mesenchymal hamartoma

Hepatic mesenchymal hamartoma is the second most common benign hepatic tumour in children. This rare tumour is seen in children less than 2 years of age and more common in males (2:1). The right hepatic lobe is much more frequently affected than the left. When diagnosed, these lesions are commonly >10 cm.⁴² Depending on tumour size, clinical presentation is variable and may include a palpable abdominal mass, anorexia and weight loss. Large tumours can obstruct the extrahepatic bile ducts and inferior vena, leading to jaundice and lower extremity oedema.⁴³

Imaging features of this tumour depend on the predominance of cystic or solid components. At ultrasonography, they appear as well-defined multicystic masses. The cystic components are variable in size and separated by echogenic septa. Calcifications and foci of necrosis or haemorrhage are rare.⁴² At MRI, the cystic components are generally hyperintense on T_2 weighted images and of variable signal intensity on T_1 weighted images, depending on the proteinaceous content within the cyst.⁴³ Solid components appear hypointense relative to the normal liver

Figure 9. Breast hamartoma: a craniocaudal mammogram of the left breast is demonstrating a large fat-containing mass in the medial aspect of the breast (arrows). The mass is showing a thin radiopaque capsule.

parenchyma on both T_1 and T_2 weighted images owing to their fibrotic nature. After gadolinium injection, solid components and septa show a mild enhancement (Figure 10).⁴²

Biliary hamartomas

Biliary hamartomas, also known as biliary microhamartomas or von Meyenburg complexes, are benign hepatic malformations consisting of focal, disorderly collections of dilated intrahepatic bile ducts, lined by the biliary epithelium and embedded within dense fibrous stroma.⁴⁴ These tumours result from an abnormal embryogenesis of the biliary ductal system.⁴⁵

Biliary hamartomas typically appear as multiple incidentally detected rounded lesions of varying size, usually measuring <1.5 cm, uniformly distributed throughout the liver. Solitary lesions have also been described. On ultrasound, they appear as multiple small hypoechoic or hyperechoic foci, with comet-tail artefacts. Differences in echogenicity depend on the size of the dilated ductal component; while isolated cysts appear anechoic, numerous adjacent microcysts can appear echogenic and resemble small solid nodules. On CT, they appear as small, well-defined, hypoattenuating and non-enhancing lesions (Figure 11). At MRI, they are hypointense on T_1 weighted images, hyperintense on T_2 weighted images and occasionally present with a thin peripheral rim of enhancement. On heavily T_2 weighted images, the signal intensity of these lesions increases further and approaches that of the cerebrospinal fluid.^{44,45} At MR cholangiography, the multiple tiny cystic lesions demonstrate no communication with the biliary tree. The differential diagnosis for biliary hamartomas includes metastatic disease, multiple simple hepatic cysts, autosomal-dominant polycystic kidney disease and Caroli disease.^{44,45}

Splenic hamartomas

Splenic hamartoma is a rare, benign primary neoplasm of the spleen composed of anomalous splenic red pulp elements without organized lymphoid follicles. Most cases are sporadic, but may occur in association with tuberous sclerosis (TSC).

Most of these lesions result in no symptoms and are diagnosed incidentally.⁴⁶

On ultrasonography, splenic hamartomas are typically solid homogeneous masses, hypoechoic relative to the normal adjacent splenic parenchyma. At colour Doppler, these lesions often demonstrate increased blood flow.⁴⁶ At CT, hamartomas can be difficult to detect, as they are usually isointense to normal splenic tissues on non-contrast and contrast-enhanced images. Sometimes, the only finding is a contour abnormality.⁴⁶ At MRI, splenic hamartomas are well defined with smooth borders, clearly separated from normal splenic tissues. They are typically isointense relative to normal splenic parenchyma on T_1 weighted images, heterogeneously hyperintense on T_2 weighted images and show heterogeneous enhancement on early post-contrast T_1 weighted images. Enhancement becomes more homogeneous on delayed imaging.⁴⁷

Genitourinary hamartomas

Angiomyolipoma

Angiomyolipoma (AML) is the most common benign solid renal neoplasm and is composed of vascular, smooth muscles and fat elements.⁴⁸ In 50–80% of the cases, these lesions occur sporadically. The remaining cases are part of syndromic conditions such as tuberous sclerosis. Sporadic AMLs develop during the fourth–sixth decades and are more common in females than in males.⁴⁹ AMLs are usually small and solitary lesions, with no associated symptoms. Large lesions are prone to trauma or spontaneous haemorrhage and may present with flank pain, a palpable mass and haematuria. In patients with tuberous sclerosis, AMLs develop earlier (third–fourth decades), demonstrate no gender predilection and tend to be multiple and bilateral. Sporadic and syndromic forms are histologically identical.⁴⁸

Imaging features depend on the predominance of the fatty component. Lipid-poor AMLs account for <5% of all renal AMLs and may be difficult to differentiate from other solid renal tumours.⁴⁸

Figure 10. Hepatic mesenchymal hamartoma in a young infant: the axial T_2 weighted (a) and post-contrast T_1 weighted (b) MR images of the abdomen are demonstrating a large multicystic mass arising from the liver. No enhancing nodules are seen. Case courtesy of Christine Menias, MD.

Figure 11. Biliary hamartomas (von Meyenburg complex): a contrast-enhanced CT image of the abdomen is demonstrating innumerable fluid-attenuating lesions throughout the hepatic parenchyma. There are no internal septations or nodularity. Case courtesy of Srinivasa Prasad, MD.

At ultrasonography, AMLs typically appear as diffusely hyperechoic masses. At CT, these lesions are well-defined, cortical masses of predominant fat attenuation, with heterogeneous attenuation secondary to the presence of haemorrhage or fibrosis within the lesion. The degree of contrast enhancement also depends on the amount of soft and vascular tissues (Figure 12).⁵⁰

At MRI, AMLs can be reliably diagnosed by demonstrating the presence of macroscopic fat on fat-suppressed images. The use

Figure 12. Multiple bilateral renal angiomyolipomas (AMLs): a transaxial contrast-enhanced CT image of the abdomen is showing multiple heterogeneous lesions arising from the bilateral kidneys (black arrows), many of which are demonstrating foci of fat attenuation. A predominantly fatty lesion is seen in the right kidney (white arrowhead). Arising from the anterior aspect of the right renal interpolar region is an enhancing lesion that is predominantly homogeneous and compatible with a lipid-poor renal AML (white arrow).

of in-phase and opposed-phase imaging is especially helpful in the diagnosis of very small AMLs, which can be difficult to diagnose with fat-selective suppression techniques. A characteristic India ink artefact seen on opposed-phase images makes small lesions more conspicuous.⁵¹

Adrenal hamartoma

Adrenal hamartoma or myelolipoma is a relatively uncommon benign tumour composed of variable amounts of mature adipose tissues and scattered islands of haematopoietic elements. They account for 3–5% of all primary adrenal tumours and are the most common fat-containing tumours of the adrenal gland.^{52–54} Myelolipomas are usually not hormonally active and are most commonly asymptomatic, unless they are large enough to cause a local mass effect or rupture spontaneously. Rupture results in retroperitoneal haemorrhage and flank pain. Very rarely, they are associated with adrenal functional disorders such as congenital adrenal hyperplasia and Cushing syndrome.⁵⁵

At ultrasonography, myelolipomas typically appear as a heterogeneous mass of mixed hyperechoic and hypoechoic areas determined by the fatty and myeloid components, respectively. At CT, they appear as well-delineated, heterogeneous masses with areas of fat attenuation. Small punctate calcifications may be seen in 25–30% of cases. At MRI, these lesions are heterogeneously hyperintense on T_1 weighted images and show signal drop out on fat-saturated sequences.⁵⁵

Retrorectal cystic hamartomas

Retrorectal cystic hamartomas, or tailgut cysts, are rare congenital cystic lesions that arise from caudal embryonic vestiges, located between the rectum and sacrum. They are most commonly found in middle-aged females, but may manifest at any age. Retrorectal cystic hamartomas are asymptomatic in 50% of the cases. When present, symptoms depend on the lesion size and/or mass effect upon adjacent structures. Infection is a potential complication and may lead to formation of a perianal fistula or rectal bleeding.⁵⁶

At ultrasonography, they appear as a unilocular or multilocular retrorectal cystic lesions, sometimes with internal echoes owing to mucoid or inflammatory debris. CT shows a well-margined, thin-walled, unilocular or multilocular, hypoattenuating, non-enhancing mass in the retrorectal space. At MRI, they appear as well-circumscribed, thin-walled hypointense lesions on T_1 weighted images and homogeneously hyperintense lesions on T_2 weighted images. A superinfected retrorectal cystic hamartoma may be suspected when perilesional inflammatory changes are seen. In addition, wall thickening and enhancement, or an air–fluid level, may be seen in these cases.^{56,57}

Malignant degeneration is rarely seen and results most commonly in adenocarcinoma. Because of this, differentiating retrorectal cystic hamartomas from other benign cystic lesions that may arise in this region is particularly important. Such lesions include dermoid and epidermoid cysts, anterior meningoceles and rectal duplication cysts. Cystic lymphangiomas also have a similar appearance. Cystic lymphangiomas and retrorectal cystic hamartomas are often multilocular, whereas the other

mentioned cystic lesions are commonly unilocular. Complete surgical excision is the treatment of choice for retrorectal cystic hamartomas.⁵⁷

Musculoskeletal hamartomas

Lipomatosis of a nerve

Lipomatosis of a nerve is the current term designated by the World Health Organization Classification of Tumours to describe a rare, tumour-like condition characterized by a fusiform enlargement of a nerve due to anomalous proliferation of the fibrofatty tissue within the epineurium and perineurium.^{58,59} In the past, this condition has been referred to as fibrolipomatous hamartoma of a nerve or neural fibrolipoma. It most commonly affects the upper extremity (78–96% of cases) with a marked predilection for the median nerve (85% of reported cases) and its branches.⁶⁰ Fibrolipomatous hamartomas may be associated with macrodactyly in the distribution of the affected nerve in up to two-third of cases, characterized by an osseous overgrowth and a proliferation of subcutaneous fat.⁵⁸ Onset of manifestations commonly occurs before the age of 30 years, often at birth or early childhood. The spectrum of clinical presentations varies from a soft, slowly enlarging asymptomatic mass to progressive neurologic deficits associated with dysmorphic changes of the compromised nerve.⁵⁸

The typical MRI appearance of lipomatosis of a nerve is pathognomonic. T_1 weighted images show low-intensity, tubular structures representing the individual nerve fascicles surrounded by high-signal intensity fat within the expanded nerve sheath (Figure 13). T_2 weighted sequences do not typically show increased signal in the nerves and on T_2 weighted fat-suppressed images or short tau inversion-recovery sequences, the nerve appears homogeneously hypointense.^{58,60}

Figure 13. Fibrolipomatous hamartoma of the sciatic nerve: an axial T_1 weighted MR image through the left gluteal region is demonstrating increased thickness and fatty infiltration of the sciatic nerve (arrow), resulting in a “coaxial cable” appearance.

SYNDROMES WITH MULTIPLE HAMARTOMAS

Carney triad

Carney triad is defined by the development of extra-adrenal paragangliomas, gastrointestinal stromal tumours (GISTs) and pulmonary chondromas. Carney triad is a non-hereditary, sporadic generally indolent condition with a long natural history, affecting young females of under 30 years of age. Although an aetiology has not been established, the disorder is most likely genetic. Given the rarity of the disorder, prevalence is unknown. Carney triad must be differentiated from the similar dyad of paraganglioma and GIST, or Carney–Stratakis syndrome. Carney–Stratakis syndrome is an autosomal-dominant disorder that affects both males and females and is likely more frequent than Carney triad.^{61,62}

Only one-fifth of patients with Carney triad present with the three tumours. Most present with two, usually GIST and pulmonary chondromas. About 12% of these patients also present with adrenocortical adenomas.⁶²

GISTs are usually the commonest presenting lesions (75%). Clinically, they can manifest with upper gastrointestinal bleeding. Occasionally, an asymptomatic upper abdominal mass can be palpated (Figure 14a).⁵¹

Pulmonary chondromas are the second most common tumours in these patients (15%). Most cases are asymptomatic and are found incidentally in the work-up of metastatic disease following diagnosis of gastric GIST.⁵¹ These tumours do not impair lung function and do not require treatment or follow-up. They are typically multiple and composed of cartilage and bone, surrounded by a fibrous pseudocapsule and contain no adipose tissue and other histologic characteristics of pulmonary hamartoma. While these tumours may resemble pulmonary hamartomas on both imaging and histologic evaluation, designation as a chondroma is clinically important, as this may lead to the diagnosis of Carney triad (Figure 14b).⁶³

Paragangliomas represent the third most common tumour in patients with Carney triad. These tumours are distributed equally in the head and neck, thorax and abdomen. About two-third of the cases reported in one patient series presented with symptoms and signs of catecholamine excess or symptoms associated with local mass effect (dyspnoea, nerve palsy, tinnitus).⁵¹

Tuberous sclerosis complex

Tuberous sclerosis is a genetic, variably expressed, neurocutaneous disease that can present with circumscribed, benign, non-invasive lesions in any organ.⁶⁴ The classic clinical triad is that of facial adenoma sebaceum, epilepsy and mental retardation.³⁰ The disorder has an approximate birth rate of 1/6000. The mode of inheritance is autosomal dominant, with a penetrance of 95% and variable clinical manifestations.⁶⁵ Mutations in the TSC 1 and TSC 2 genes lead to abnormal control of cell growth, resulting in tumour formation.³⁰ Most commonly, tumours are seen in the skin, brain, kidneys, lungs and heart. These can lead to extensive parenchymal replacement

Figure 14. Gastrointestinal stromal tumour (GIST) and pulmonary chondroma in a patient with Carney triad: the contrast-enhanced CT of the abdomen (a) is showing a well-delineated endophytic soft-tissue density mass extruding into the gastric lumen in the region of the stomach fundus (arrow). The patient presented two other similar masses (not shown). CT of the chest in the same patient (b) is demonstrating a large, lobulated left upper lobe mass with coarse foci of calcification. In the setting of multiple GISTs, and given the CT appearance of the pulmonary lesion, this is compatible with a pulmonary chondroma.

by a variety of cell types, resulting in organ dysfunction or failure.⁶⁴ A series reported by Mayo Clinic showed that over 90% of patients had skin lesions, 90% patients had symptoms related to central nervous system (CNS) pathology, 70–90% patients had renal pathology and about 50% patients had retinal angiomas.^{64,66} In spite of advances in treatment, approximately 40% of patients die by age 35.³⁰

Neurocutaneous manifestations are the most consistent disease features, affecting about 90% of patients. CNS complications include epilepsy, cognitive impairment, challenging behavioural problems and autism.⁶⁴ The most frequent CNS manifestations include subependymal nodules and cortical tubers, which are associated with seizures and developmental delay (Figures 2 and 3).¹¹

Among thoracic manifestations of disease, cardiac rhabdomyomas are the most frequent in newborns. While most are asymptomatic,

Figure 15. Lymphangioleiomyomatosis (LAM) in a patient with tuberous sclerosis: a high-resolution axial CT image of the chest is demonstrating innumerable somewhat uniform cysts throughout the lung parenchyma, with findings compatible with TSC-associated LAM.

some cases can present with arrhythmia, non-immune fetal hydrops and death. Most newborns with cardiac rhabdomyomas will eventually be diagnosed with TSC (Figure 8).⁶⁴

Pulmonary manifestations of TSC include LAM and MMPH. LAM is characterized pathologically by a hamartomatous proliferation of smooth muscle-like cells in the lymphatics and small airways, leading to air trapping and extensive parenchymal replacement by cysts. LAM can present sporadically in patients without TSC, affecting females exclusively and are associated with mutations of the TSC 2 gene. Sporadic LAM is considered a form fruste of TSC. On the contrary, TSC-associated LAM can be seen in males. The prevalence of LAM in patients with TSC ranges between 1% and 3%, and up to 35% in females with TSC. Early manifestations include dyspnoea, atelectasis, cough and chest pain. Complications of LAM include chylothorax, spontaneous pneumothoraces and haemoptysis. The imaging manifestations of LAM include multiple thin-walled cysts distributed uniformly throughout the lung (Figure 15). Cysts may decrease in size on expiratory images. Pulmonary hamartomas and foci of MMPH are relatively frequent manifestations of disease (Figure 7).^{30,64}

Renal AMLs are the most common intra-abdominal manifestations of TSC, found in 70–90% of patients (Figure 12). Spontaneous or trauma-related bleeding of these tumours represents the leading cause of death in patients with TSC. Resection or embolization is recommended if >4 cm in diameter. As previously discussed, AMLs can entirely replace the renal parenchyma. A percentage of patients with TSC can develop renal cysts. These are usually asymptomatic, unless they are in patients with contiguous deletions in TSC 2 and PKD 1. In the latter set of patients, replacement of the renal parenchyma by multiple and large cysts results in renal failure by early adulthood. Renal cell carcinoma is seen in 2–4% of patients with TSC.⁶⁴ A recent study by Yang *et al*⁶⁷ showed that approximately one-half of these neoplasms are of papillary architecture (TSC-associated papillary renal cell carcinoma) and nearly one-third of the neoplasms were found to be a similar to a hybrid oncocytic/chromophobe tumour. The remaining neoplasms were deemed unclassifiable.

Figure 16. Proteus syndrome in a young female: a photograph of the patient hands (a) is showing an abnormal asymmetric growth of the left index finger and to a lesser degree of the distal aspect of the left middle finger. The frontal radiograph of the left hand (b) is showing an asymmetric growth of the left index finger phalanges and thickening of the overlying soft tissues.

Proteus syndrome

Proteus syndrome is a rare condition that results in a multifocal overgrowth of tissue arising from any of the three germinal layers. The cause of this syndrome remains unknown, but a sporadic mutation in the genes regulating production of tissue growth factor receptors has been postulated.⁶⁸

Organs are affected randomly and grow out of proportion to the rest of the body. Asymmetric features may be absent or subtle at birth, but progress during childhood. Clinical findings in patients with Proteus syndrome include an asymmetric overgrowth of long bones, asymmetric macrocephaly, vertebral anomalies, hyperostosis, partial gigantism of hands (Figure 16) or feet, cutaneous nevi, lipomas and vascular malformations.

While there is rapid progression of the disease during childhood, this may slow or even stabilize once patients reach adolescence. A subset of patients die prematurely. Common causes of death include respiratory failure and pulmonary embolism.⁶⁹

CONCLUSION

Hamartomas can occur sporadically or as part of a syndrome. They can affect virtually every system; however, they are usually not associated with significant morbidity. Knowledge of the clinical and imaging manifestations of the hamartomas in different organs is crucial to avoid misdiagnosis, as they often mimic other neoplasms. Radiologists must be familiar with syndromes that present with hamartomatous lesions, as imaging may offer the first clue to diagnosis in some of these patients.

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