Original Article

Hamartomas of Body: A Revisited Entity - An Experience of a Tertiary Care Hospital

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Abstract

Introduction/Background: Hamartoma is a mass of disorganized tissue indigenous to the particular site. Although traditionally considered as developmental malformations, many hamartomas have clonal chromosomal aberration that is acquired through somatic mutation, thus now considered to be neoplastic. They arise virtually in all organs, either sporadically or in association with autosomal dominant syndrome. **Materials and Methods:** A retrospective study was carried out in a tertiary care health institute for 3-year period (January 2013 to December 2016), which included all visceral hamartomas from head to toe. Detailed clinicoradiological and pathological examination was done along with ancillary tests for definite diagnosis. **Observation:** The study included nine cases, categorized site wise as head and neck (one case of cystic lymphangioma), cardiothoracic (one case of chondroid hamartoma), gastrointestinal tract (GIT) (one case of Brunner's gland hamartoma), hepatic (one case of cystic lymphangioma), and genitourinary tract (four cases of angiomyolipoma [AML] and one case of myelolipoma). The age ranged from 1 year to 70 years showing a male predilection. The tumors were variable sized ranging from 0.5 to 20 cm in dimension either solitary or multiple. Some large tumors clinically masqueraded as malignant tumors and presented with complications. The postsurgical course and prognosis of all patients were uneventful. **Conclusion:** Hamartomas are usually not associated with significant morbidity but for the size and location of the tumor. Despite slow-growing and self-limiting behavior, some predispose to malignancy especially in the epithelioid AML and familial GIT hamartoma or may be seen associated with malignancy in syndromic forms.

Keywords: *Brunner's gland hamartoma, developmental malformation, epithelioid angiomyolipoma, hamartoma, malignancy*

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Introduction

The term hamartoma is derived from Greek word of "hamartia" referring to a defect or an error. It was originally coined by Albrecht in 1904 to denote developmental tumor-like malformation.[1,2] It can be defined as a nonneoplastic, uni/multifocal, developmental malformation, comprised of mixture of cytologically normal mature cells and tissue, indigenous to the anatomic location, showing disorganized architectural pattern.[3,4] They arise virtually in all organ systems, either sporadic or syndromic.[5]

Few hallmark features of hamartoma included are:[4,6]

- Developmental malformation may present at birth as solitary/multiple
- Self-limited growth, coordinated with surrounding tissue
- Not a true neoplasm but a true neoplasm can develop in hamartoma

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- Association with chromosomal abnormalities and syndromes.

These are derived from any of the embryonic lineages, most common being mesoderm, but not clonally derived like neoplasm.[7]

Materials and Methods

A retrospective study was conducted in the pathology department of a tertiary health institute over a period of 3 years (January 2013 to December 2016), which included all the visceral hamartomatous lesion.

Total of nine cases were included in the study which were further categorized as head and neck, cardiothoracic, gastrointestinal tract (GIT), hepatic, as well as genitourinary tract (GUT) hamartomas. Detailed clinical history and radiological findings were archived from the hospital registry and taken into consideration. Some of the cases, especially the GUT, GIT, and cardiothoracic category, were clinically and radiologically misdiagnosed as carcinoma because of large size, variegated appearance, and multiplicity in some.

This is a retrospective study done on paraffin-embedded biopsy tissue blocks retrieved from archives of department of pathology. For this before surgery, informed and written consent was taken for each case. This study does not require any ethical clearance certificate as it does not deal with the patients directly to carry out the proposed study. The institutional ethics committee has been intimidated, and an approval letter stating that the same has been obtained (ref. no: DRI/IMS. SH/393/2020, date – 06/10/2020).

Limitations

Due to the relatively low sample size, statistical analysis was not performed in the study.

Results

It was observed that maximum case incidence occurred in GUT category (five cases) followed by one case each in all other parts, namely head and neck, cardiothoracic, GIT, and hepatic sites.

Head-and-neck hamartoma

A 24-year-old male presented as an acute onset swelling of size 7 cm × 5 cm × 2 cm with neck stiffness, in the preauricular region. Ultrasonography of neck revealed a well-defined heterogeneous hypoechoic space-occupying lesion with internal cystic spaces and low vascularity suggesting hemangioma. The patient was advised for fine-needle aspiration cytology which yielded 5 mL of hemorrhagic fluid with reduction of swelling. Cytosmears revealed occasional salivary gland acini with few naked nuclei over hemorrhagic background, based on which diagnosis of vascular lesion was made. Gross specimen showed a circumscribed solid cystic tumor of 2.3 cm × 2 cm × 2 cm size in the parotid gland, with cystic spaces on cut section filled with mucoid material. Microscopy showed a well-circumscribed lesion comprised of large cystic spaces lined by attenuated endothelium, containing proteinaceous material and lymphocytes, surrounded by lymphoid aggregates, fibrosis, and normal salivary gland structure [Figure 1]. Thus, the diagnosis of intraparotid cystic lymphangioma was made.

Cardiorespiratory hamartoma

The second case presented with 6-month history of cough and dyspnea in a 48-year female. The chest X-ray and computed tomography (CT) scan showed a 8 cm × 4.5 cm fairly well-defined perihilar mass in the upper lobe of left lung with popcorn pattern of calcification, diagnosed as bronchogenic carcinoma. Microscopy of the lobectomy specimen showed predominantly large lobules of mature cartilage separated by abundant adipose tissue, small amount of fibromyxoid stroma enclosing cleft-like spaces lined by respiratory epithelium. No malignancy was noted. Thus, the diagnosis of chondroid hamartoma was made.

Gastrointestinal tract hamartoma

The third case occurred in a 30-year-old male presented with intermittent bilious vomiting, and pain abdomen showed extensive multiple enhancing polypoid lesions in duodenum with near-complete narrowing and jejunojejunal intussusception. Upper GI endoscopy showed multiple duodenal polyps in the duodenum. Thus, pancreaticoduodenectomy was done which revealed multiple duodenal polyps (average 120 in numbers), both small, large, sessile to pedunculated, the size varying from

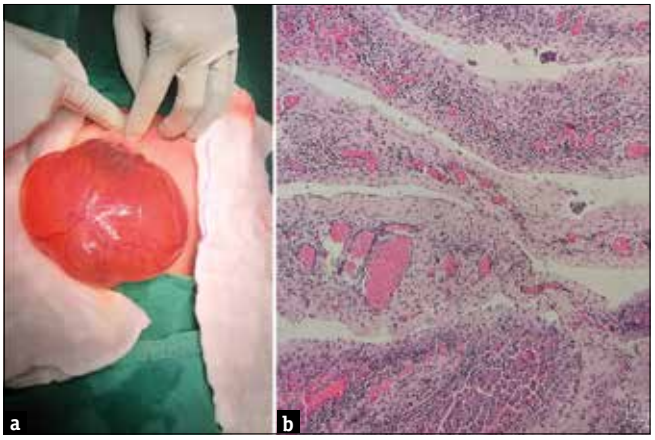

Figure 1: (a) Intraoperative cystic mass of the liver containing serosanguinous fluid, (b) the tumor is composed of cystically dilated lymphatic spaces showing endothelial cell lining, lymphoid aggregates, and partially invested by smooth muscles (×100)

3.2 cm × 2 cm to 0.5 cm × 0.3 cm × 0.3 cm. Histopathology examination showed marked hyperplasia of Brunner's gland, some of which were cystically dilated and placed in lobular fashion surrounded by hyperplastic smooth muscle vessels, lymphoid aggregates and fat predominantly, located in lamina propria and submucosa. Thus, the diagnosis of Brunner's gland hamartoma was made.

Hepatic hamartoma

The fourth case was seen in a 2-day-old male child presenting with pain abdomen and a large right hypochondriac mass. Ultrasound abdomen showed a large intraperitoneal cystic lesion arising from under surface of liver, with posterior displacement of bowel loops, diagnosed as mesenteric cyst. The cystectomy specimen received showed a cyst measuring 9 cm × 4.5 cm with papery thin wall containing whitish mucoid material. Microscopic examination showed the cyst wall lined by flattened endothelium containing and surrounded by lymphoid aggregates surrounded by liver parenchyma and bile ducts embedded in fibrocollagenous stroma. Thus, the diagnosis of hepatic cystic lymphangioma was given.

Genitourinary tract hamartoma

The genitourinary hamartoma predominantly comprised of four cases of renal angiomyolipoma (AML) (four cases) and one case of adrenal myelolipoma. The age incidence of AML varied from 50 to 60 years showing equal sex incidence, three of which presented with hemoperitoneum illustrated in Table 1.

Also included in this group was a 62-year-male presented with right flank pain and dyspepsia showing a well-circumscribed heterogenous mass of 10.5 cm × 8 cm × 7 cm. CT scan shows hyper and hypoechoic areas with fat attenuation and punctate calcification. Gross examination of the adrenalectomy specimen shows a tumor with variegated, predominantly fatty areas on cut sections. Microscopy showed variable amount of mature adipocytes with scattered hematopoietic elements inclusive of erythroid, myeloid series cells, and few megakaryocytes [Figure 2]. Thus, the diagnosis of myelolipoma was rendered.

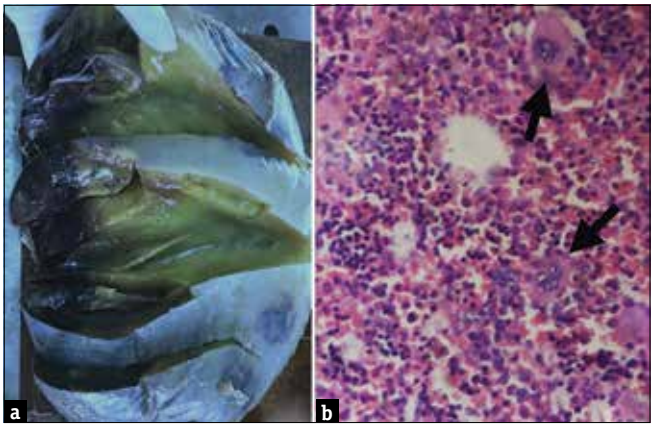

Figure 2: (a) Gross finding of a large nonencapsulated adrenal mass showing areas of hemorrhage and bright yellow adipose tissue area. (b) Microphotograph showing islands of hematopoietic cells comprising of normal trilineage hematopoiesis, with markedly increase in megakaryocytes (arrow mark) (×100)

Table 1: Clinicoradiological and pathological findings of renal angiomyolipoma

	Case 1	Case 2	Case 3	Case 4
Age	60	56	53	60
Sex	male	male	Female	Female
Tumor size	13.5 × 11 × 8.5 cm	20 × 14 × 8.5 cm	2.2 × 4 × 3.5 cm	10.5 × 9 × 7 cm
Clinical features	Acute pain abdomen	Pain right flank region	Flank pain & haematuria since one month	Acute pain abdomen with vomiting
Radiological findings	Left renal exophytic mass with foci of fat haemorrhage & hemoperitoneum of size 13.5 × 11.8 × 8.5cm in lower pole with capsular rupture.	20 × 14 × 8.5cm mass in lower pole of right kidney with internal as well as retroperitoneal haemorrhage	Heterogenous lesion of 4 × 3.5 × 2.2cm, right kidney with central lobulated hypodense area of fat attenuation	Heterogenous lesion of 10.5 × 9 × 7cm in lower pole of left kidney with partial rupture of capsule and fascia of gerota.
Radiological diagnosis	Perinephric hamartoma	Wanderlich syndrome	Renal cell carcinoma	Ruptured AML
Pathological diagnosis	Triphasic tumour composed of mature adipose tissue, myoid spindle cells and variable sized blood vessels with focal rupture of capsule. Diagnosis - AML	Triphasic pattern of fat, vessel as well as myoid spindle cells with capsular rupture. Diagnosis - AML	Predominant fatty area with small foci of blood vessels lined by myoid cells Diagnosis - AML	Predominant mature adipose tissue lobules with smooth muscle radiating from vessel wall showing epithelioid morphology (15%). No atypia/mitosis/necrosis. Diagnosis - AML
Current status	Free of disease	Free of disease	Free of disease	Stable

AML: Angiomyolipoma

On follow-up, after 1 year, all but duodenal Brunner's gland hamartoma which was lost to follow-up were asymptomatic and did not show recurrence or metastasis.

Discussion

A hamartoma is a tumor-like lesion comprised of abnormal mixture of normal components indigenous to the site. They can arise virtually in all organ systems either sporadically or in association with syndromic entities, some having genetic basis.[5]

System by system review categorizes hamartoma according to central nervous system, head and neck, cardiothoracic, GIT, GUT, hepatic, and musculoskeletal origin.[5]

The head-and-neck hamartomas are classified based on tissue of origin into three groups, epithelial, connective tissue, and miscellaneous category.[8] Connective tissue hamartoma is a broad category showing varied tissue origin, namely vascular, lymphatic, neural, and osseous.[8] Cystic lymphangioma is included in this category and has to be differentiated from Warthin tumor, cystic pleomorphic adenoma, and nonneoplastic cysts like retention cyst because of parotid location. Aid of vascular endothelial growth facto-3, D2-40, and CD31 in addition to histopathology helps to confirm the diagnosis.[9]

Cardiothoracic category of hamartoma includes pulmonary chondroid hamartoma, accounts for 6%–8% of solitary pulmonary nodules, presenting with coin lesion.[10] The common age group affected is 4th to 7th decade showing male predominance. Ninety percent tumors are peripheral parenchymal in location while <10% are central endobronchial, maximum dimension ranging from 1 to 4 cm.[11-13] According to the WHO 2016 classification of lungs, chondroid hamartoma is a major subgroup of mesenchymal tumor currently designated as pulmonary hamartoma.[14] The size of hamartoma was large 8 cm × 4.5 cm showing a lobulated solitary nodule showing popcorn calcification, On CT scan, the differential diagnosis includes bronchial chondroma, cystic blastoma, and primary lung carcinoma.

Histologically, it is differentiated by absence of neoplastic tissue. Chondroid hamartomas can histologically mimic bronchial chondroma but is differentiated by lack of mixture of mesenchymal elements and it lies in continuity with bronchial cartilage in the later. Similarly, cystic blastomas are distinguished from chondroid hamartoma by presence of cambium layer of embryonic mesenchyme adjacent to the epithelial lining along with the presence of immature mesenchymal elements in the former.[12]

Hamartomatous tumors in GIT include sporadic type (solitary Peutz–Jeghers polyp/juvenile polyp) or familial polyps such as Peutz–Jeghers syndrome, juvenile polyposis, or Cowden's disease.[15] Brunner's gland hamartoma is a rare entity commonly occurring in 4th to 6th decade without sex predilection.[16] Multiple Brunner's gland hamartomatous polyps were encountered in duodenum in our study. Brunner's gland hamartoma is the preferred term for solitary lesion which shows the presence of adipose tissue, smooth muscle bundles, and lymphoid tissue along with Brunner's gland hyperplasia. Lesions showing microscopic features of Brunner's gland hyperplasia and size >1 cm are called Brunner's gland adenoma. Brunner's gland hamartoma can show foci of high-grade dysplasia and even have carcinomatous transformation hence termed Brunner's gland adenoma.[17]

AML was considered to be the most common renal hamartomas in older literature. However, according to the WHO (2016),[18] it is classified as a most common mesenchymal tumor, under PECOMA group. The cell of origin of neoplastic cells is perivascular epithelioid cells divided into triphasic (fat rich/fat poor type) and monophasic type.[19] 50%–80% of AML are sporadic while rest associated with tuberous sclerosis (with tuberous sclerosis complex [TSC]-1 and TSC-2 gene).[20] It occurs in 4th to 6th decade more common in females, and due large size and associated complication of hemorrhage and hemoperitoneum, thus stimulate renal cell carcinoma (RCC), especially the fat poor type. Epithelioid variant of AML has a malignant behavior, including recurrence and metastasis. The worrisome histologic features of AML are large size, hemorrhage, coagulative necrosis, and atypical mitosis, thus contribute to the misdiagnosis as RCC or metastatic melanoma and are differentiated by negative epithelial markers and positive for S-100 and HMB-45. The RCC unclassified type associated with t (X:1p11)/TFE3 may rarely be positive for HMB-45 or negative cytokeratin stain similar to AML, which is also seen in renal AML but differentiated by CD-10 stain and molecular marker of TFE3.[21,22]

Adrenal hamartomas are uncommon accounting for 3%–5% of primary adrenal tumors and are mostly asymptomatic unless large size is achieved. Chronic stimulation by adrenocorticotropic hormone has been implicated in the origin of adrenal myelolipoma. Increasing incidence with advancing age (5th–7th decade) and stress has been cited to play a role. An increasing incidence of large AML has been reported in patients with hemolytic anemia due to stimulation of erythropoietin.[22]

The syndromic types of multiple hamartomas which need special mention are Carney triad, TSC, and Proteus syndrome, as they are associated with multiple malignancies.

Hamartomas are local malformations which resemble a neoplasm but are differentiated based on the absence of monoclonality. Many hamartomas because of their peculiar behavior need a long-term clinicoradiological follow-up and further molecular study, especially in syndromic types of multiple hamartomas.

Conclusion

Hamartoma is usually not associated with significant morbidity but for the size and location of the tumor. There is evolution of some of the hamartomas as to neoplastic category included in recent WHO (2016) class of tumors because of clonality. This includes renal AML and pulmonary lymphangioleiomyomatosis. Despite the slow-growing and self-limiting behavior, some predispose to malignancy especially familial GIT hamartoma or may be seen associated with malignancy particularly in syndromic forms. In recent times, the concept of chondroid hamartomas is seen to be associated with abnormal karyotypes which points the neoplastic nature of the lesion.

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Conflicts of interest

There are no conflicts of interest.

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