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A RARE CASE OF TUBEROUS SCLEROSIS WITH HIGH GRADE PAPILLARY SEROUS CARCINOMA

Divya Madhala[1], Priyathersini Nagarajan[1], Balasubramanian Venkitaraman[2]

1. Department of Pathology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra Institute of Higher Education and Research, Chennai, India

2. Department of Surgical Oncology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra Institute of Higher Education and Research, Chennai, India

Corresponding Author: Priyathersini Nagarajan,

Associate Professor, Department of Pathology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra Institute of Higher Education and Research, Chennai, India

Email: nagarajan.priyathersini@gmail.com

Tel: 91 9443881481

Authors ORCID:

Divya Madhala: 0000-0001-5924-1157

Priyathersini Nagarajan: 0000-0003-3420-5752

Balasubramanian Venkitaraman: 0000-0002-3983-944X

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Abstract

Tuberous sclerosis(TSC) is an inherited autosomal dominant disease. Many systems in the body are affected. However, the occurrence of malignancy in these patients is considered very rare, the most common being renal cell carcinoma. The occurrence of high grade papillary serous carcinoma(HGSC) involving the adnexa is extremely uncommon with hardly any literature available regarding the occurrence of this malignancy in TSC patients. A 62 year old female presented radiologically with mass near the uterus involving the left tube and ovary measuring 13x10x8cm and multiple cysts in the lung diagnosed radiologically as lymphangioleiomyomatosis. Radiologically the left kidney showed a lesion measuring 14x9x7cm and the right kidney showed angiomyolipomas. USG guided biopsy was performed in the left kidney and adnexa. Following this Left radical nephrectomy along with total hysterectomy with bilateral salpingo oophorectomy(TAH with BSO) was performed. Left kidney showed a lesion measuring 16x9x10cm which was histologically diagnosed as angiomyolipoma. TAH with BSO specimen showed a 13x10x8cm lesion occupying the left adnexa. The HPE was suggestive of a HGSC. The diagnosis and treatment of TSC is complex and requires a multidisciplinary approach involving various specialists to decrease the mortality and morbidity and thus increase their survival rate.

Introduction

Tuberous sclerosis (TSC) is an inherited autosomal dominant genetic disease affecting the genes TSC1 and TSC2 and presents with varied clinical abnormalities including lesions in the skin, brain, heart, lungs and kidneys. However the occurrence of a malignancy such as high grade serous carcinoma (HGSC) is considered very rare (1). Here we present a unique and a rare case of tuberous sclerosis with presence of 2 major and 1 minor criteria diagnosed radiologically and pathologically with a coexisting high grade papillary serous carcinoma.

Case report

A 62 year old female patient came with complaints of breathlessness for 2 months and sudden onset left side pain in the lower abdomen. Magnetic resonance imaging (MRI) pelvis showed a heterogenous multilobulated mildly T2 hyperintense lesion present near the fundus of the uterus measuring 13x10x8cms (Figure 1a). Computerised tomography (CT) of the lung showed multiple randomly distributed air filled cysts present in bilateral lung parenchyma, the largest measuring 3.4x3cms (Figure 1b). A differential diagnosis of lymphangioleiomyomatosis was considered. CT of the left kidney showed a heterogeneously enhancing lesion measuring 14x9x7cm with soft tissue density and fat mixed (Figure 1c). Ultrasound (USG) of the Right kidney showed 2 well defined hyperechoic lesions in the midpole suggestive of angiomyolipomas. Also few subcentimeter cysts suggestive of simple renal cortical cysts were noted in the upper and mid pole regions of the right kidney.

USG guided biopsy of the left kidney was performed. Grossly multiple linear cores of soft tissue were received in the histopathology department. Histopathological examination (HPE) under hematoxylin and eosin (H&E) stain showed renal parenchyma with an adjacent neoplasm showing spindle shaped myoid cells, mature adipose tissue and thick

walled hyalinized blood vessels which were suggestive of a diagnosis of angiomyolipoma (Figure 2a).

USG guided biopsy was performed in the mass present in the left lateral wall of the uterus. The multiple linear cores under H&E stain showed fibrocollagenous tissue infiltrated by tumour cells arranged in sheets and forming vague glandular patterns (Figure 2b). Areas of necrosis with atypical mitosis were also seen. A diagnosis of poorly differentiated malignancy was given.

Following this the patient underwent left radical nephrectomy along with total hysterectomy with bilateral salpingo oophorectomy (TAHwithBSO) and staging laparotomy. The lower pole of the left kidney showed a single grey brown to grey yellow, solid and ill defined lesion measuring 16x9x10cms (Figure 3a). Hilar invasion and perirenal fat invasion was not present. Gerota's fascia, renal vessels and ureter were uninvolved. Histopathology showed renal parenchyma with a well encapsulated nodular neoplasm composed of spindle cells admixed with mature adipocytes and numerous proliferating blood vessels (Figure 3, b, c, d, e). Immunohistochemistry (IHC) for HMB-45 was positive and Ki67 was 1% (Figure 3f). The HPE and IHC features are that of angiomyolipoma.

TAH with BSO specimen showed a large exophytic grey brown friable lesion measuring 13x10x8cm present on the left side of the uterine wall occupying the left adnexa and replacing the left ovary and tube (Figure 4a). The HPE showed round to oval infiltrating tumour composed of neoplastic cells arranged in sheets and vague glandular pattern with increased nuclear cytoplasmic ratio and showing hyperchromasia (Figure 4b). The diagnosis was given as high grade serous carcinoma, grade G3 poorly differentiated. 4 inter aorto caval lymph nodes were positive. The ascitic fluid was negative for malignant cells. Therefore the staging was given as pT3apN1a FIGO stage IIIA. IHC for p16 (Figure 4c) and WT1 were positive and p53 showed wild type positivity. Ki67 showed 60% positivity.

Due to the presence of 2 major and 1 minor criteria, a diagnosis of tuberous sclerosis was considered along with the presence of high grade serous carcinoma. Patient is now scheduled for 6 cycles of chemotherapy using paclitaxel and carboplatin.

Discussion

Tuberous sclerosis is an autosomal dominant disorder occurring due to mutations involving the genes TSC1 which is located on chromosome 9p34, encoding the hamartin protein and TSC2 gene located on chromosome 16p13, encoding the tuberin protein (2). It occurs in 1 in 6000 - 10,000 live births. TSC affects many systems in the body including the skin, central nervous system, cardiovascular system, genitourinary system, gastrointestinal system and can present with varied manifestations (3). The clinical manifestations can present at any age in an affected individual. Among the patients affected with TSC 90% developed skin lesions (4). 80% developed renal manifestations including angiomyolipomas and renal cysts (5) (6). 40% developed lung complications due to development of lymphangioleiomyomatosis (5).

Recommendations for appropriate methods of management of patients with TSC were provided by the 2012 International Tuberous Sclerosis Complex Consensus Conference. Major and minor criteria were listed. A definite diagnosis of TSC is considered when 2 major or 1 minor and 2 major criterias are present (2).

Over the last several years, case reports of TSC patients presenting with benign and malignant lesions have been reported (7). Many different lesions like chordoma, pituitary adenoma, pancreatic endocrine tumours have been described and among malignant tumours, renal cell carcinoma is the most associated tumour in these patients.

The largest case series was described by Sauter et al where 2211 patients diagnosed with TSC were analysed (8). Among these 382 patients presented with rare manifestations and 65 patients had developed different malignancies. Though renal cell carcinoma was the

most common malignancy, the other sites where malignancies were reported include breast, colon, thyroid and ovary.

Ovarian HGSC occurring in a tuberous sclerosis patient is very rare and it needs to be differentiated from papillary serous carcinoma of peritoneum and mesothelioma (9). Review of the literature showed very few case reports of occurrence of a HGSC involving the ovary in tuberous sclerosis patients. HGSC has a very aggressive behaviour and therefore tends to have a bad prognosis.

The mammalian target of rapamycin (mTOR) signalling pathways are inhibited by hamartin and tuberin. Mutations in the genes involving these proteins result in continuous activation of mTOR which leads to development of slowly and gradually growing neoplasms. mTOR activation leads to alterations in PIK3CA where there is increased activation of AKT pathways or inactivation of the lipid phosphatase PTEN, both of which are also implicated in the development of HGSC of the ovary. Thus extensive studies are required to understand the molecular mechanisms which are common between TSC and HGSC of ovary (10). mTOR inhibitors such as rapamycin and everolimus have been developed to treat tumours such as renal angiomyolipomas and lymphangioleiomyomatosis (11) (12) (13). TSC patients with subependymal giant cell astrocytoma who are not eligible for surgery but require therapeutic intervention have been treated with everolimus (14). The treatment for HGSC of ovary involves cytoreductive surgery and the use of cisplatin and paclitaxel every 3 weeks for 6 cycles (15).

Prognosis of TSC patients with HGSC depends on the stage of the disease. The chances of curing patients in stage III/IV by current therapies including cytotoxic chemotherapy is greatly reduced.

A multidisciplinary approach involving the clinician, radiologist and a pathologist along with extensive molecular work up is extremely essential to approach, manage and have a regular follow up of tuberous sclerosis patients to decrease the mortality and morbidity and thus increase their survival rate.

Conflict of Interest:

The authors declare no conflict of interests.

References

1. Wakamiya T, Sugita Y, Hashiguchi M, Iwasaka T, Tokunaga O. Tuberous sclerosis complex associated with papillary serous carcinoma of the peritoneum, lymphangioleiomyomatosis, and angiomyolipoma. Case Rep Pathol. 2011;2011:564260. doi: 10.1155/2011/564260. Epub 2011 Oct 19
2. Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNP, Rivitti-Machado MCDM. Tuberous sclerosis complex: review based on new diagnostic criteria. An Bras Dermatol. 2018 Jun;93(3):323-331. doi: 10.1590/abd1806-4841.20186972
3. Northrup H, Koenig MK, Pearson DA, Au KS. Tuberous Sclerosis Complex. 1999 Jul 13 [updated 2021 Dec 9]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. PMID: 20301399
4. Wheless JW, Almoazen H. A Novel Topical Rapamycin Cream for the Treatment of Facial Angiofibromas in Tuberous Sclerosis Complex. Journal of Child Neurology. 2013;28(7):933-936. doi:10.1177/0883073813488664
5. Kingswood JC, Bruzzi P, Curatolo P, de Vries PJ, Fladrowski C, Hertzberg C et al. TOSCA - first international registry to address knowledge gaps in the natural history and management of tuberous sclerosis complex. Orphanet journal of rare diseases. 2014;9:182. doi: 10.1186/s13023-014-0182-9
6. Bhatt JR, Richard PO, Kim NS, Finelli A, Manickavachagam K, Legere L, Evans A, Pei Y, Sykes J, Jhaveri K, Jewett MAS. Natural History of Renal Angiomyolipoma (AML): Most Patients with Large AMLs >4cm Can Be Offered Active Surveillance as an Initial Management Strategy. Eur Urol. 2016 Jul;70(1):85-90. doi: 10.1016/j.eururo.2016.01.048. Epub 2016 Feb 9. PMID: 26873836.

7. Orlova KA, Crino PB. The tuberous sclerosis complex. Ann N Y Acad Sci. 2010 Jan;1184:87-105. doi: 10.1111/j.1749-6632.2009.05117.x. PMID: 20146692; PMCID: PMC2892799.
8. Sauter M, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. Rare manifestations and malignancies in tuberous sclerosis complex: findings from the Tuberous Sclerosis registry to increase disease awareness (TOSCA). Orphanet J Rare Dis. 2021 Jul 6;16(1):301. doi: 10.1186/s13023-021-01917-y
9. Zhou J, Iwasa Y, Konishi I, Kan N, Kannagi R, Kobashi Y, et al. Papillary serous carcinoma of the peritoneum in women. A clinicopathologic and immunohistochemical study. Cancer. 1995 Aug 1;76(3):429-36. doi: 10.1002/1097-0142(19950801)76:3<429::aid-cncr2820760313>3.0.co;2-8
10. Abdelwahab EMM, Bovari-Biri J, Smuk G, Fillinger J, McPhail D, Krymskaya VP, et al. Activated p53 in the anti-apoptotic milieu of tuberous sclerosis gene mutation induced diseases leads to cell death if thioredoxin reductase is inhibited. Apoptosis. 2021 Jun;26(5-6):253-260. doi: 10.1007/s10495-021-01670-4
11. Davies DM, de Vries PJ, Johnson SR, McCartney DL, Cox JA, Serra AL, et al. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangioleiomyomatosis: a phase 2 trial. Clin Cancer Res. 2011 Jun 15;17(12):4071-81. doi: 10.1158/1078-0432.CCR-11-0445. Epub 2011 Apr 27. PMID: 21525172
12. Franz DN, Agricola K, Mays M, Tudor C, Care MM, Holland-Bouley K, et al. Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. Ann Neurol. 2015 Dec;78(6):929-38. doi: 10.1002/ana.24523. Epub 2015 Nov 9. PMID: 26381530; PMCID: PMC5063160.
13. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 2016 Oct 29;388(10056):2153-2163. doi: 10.1016/S0140-6736(16)31419-2. Epub 2016 Sep 6. PMID: 27613521.
14. Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, et al. Tuberous Sclerosis registry to increase disease Awareness (TOSCA) -

baseline data on 2093 patients. Orphanet Journal of Rare Diseases. 2017 Jan;12(1):2. doi: 10.1186/s13023-016-0553-5. PMID: 28057044; PMCID: PMC5217262.

15. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. Int J Mol Sci. 2019 Feb 22;20(4):952. doi: 10.3390/ijms20040952. PMID: 30813239; PMCID: PMC6412907.

Figures

Figure 1

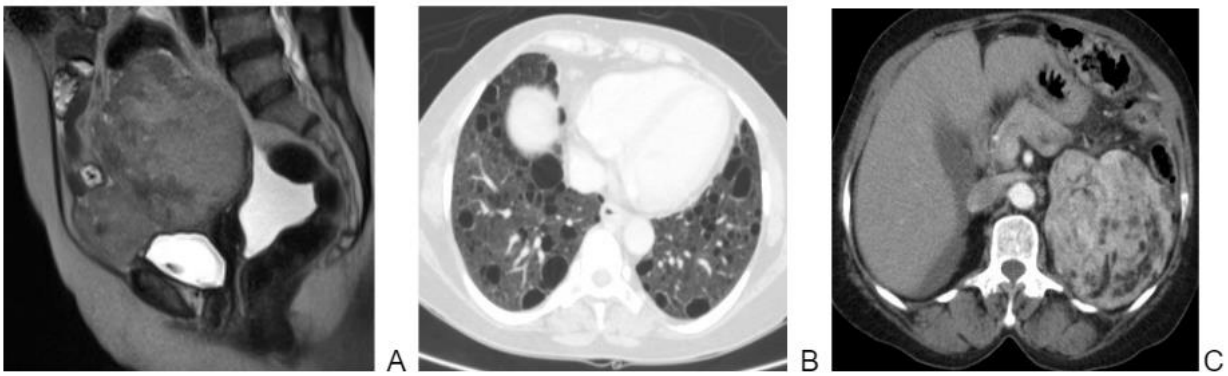


Figure 2

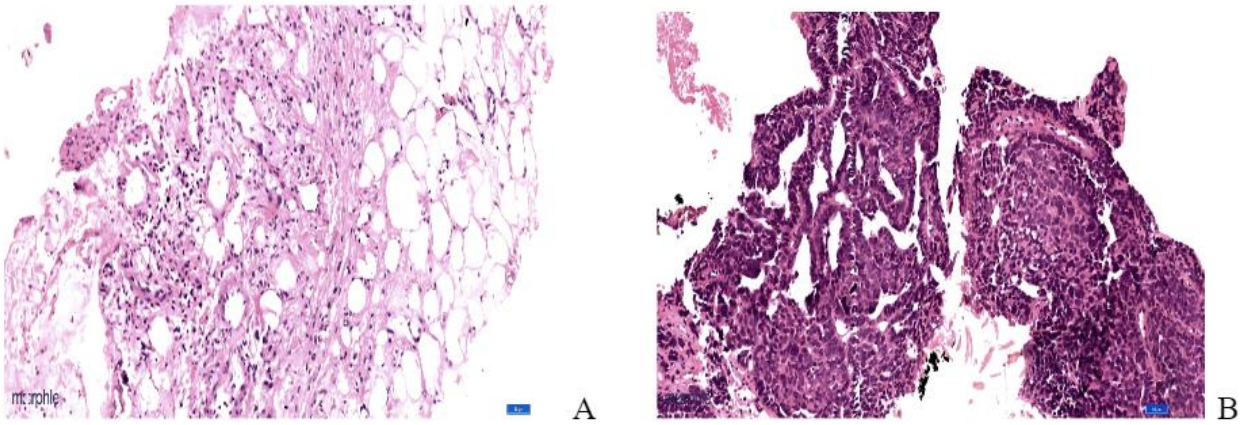


Figure 3

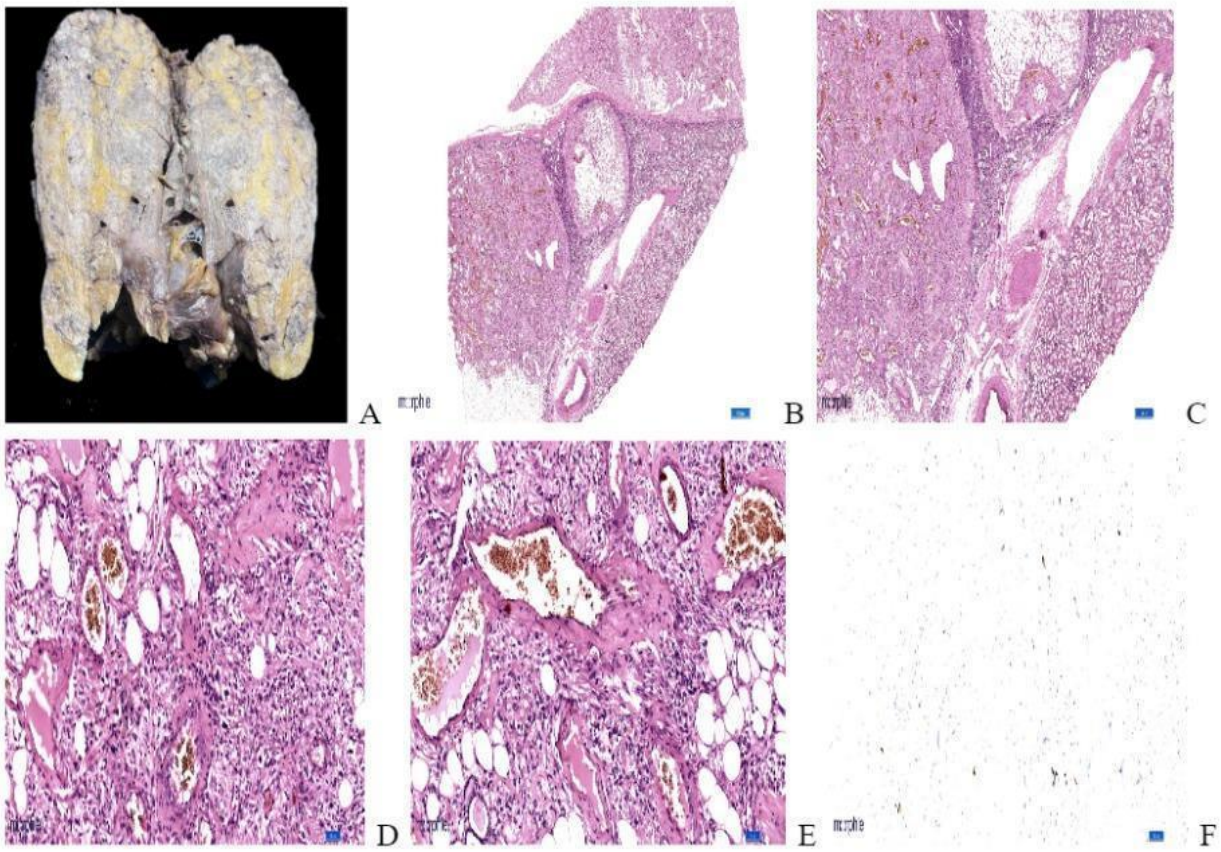
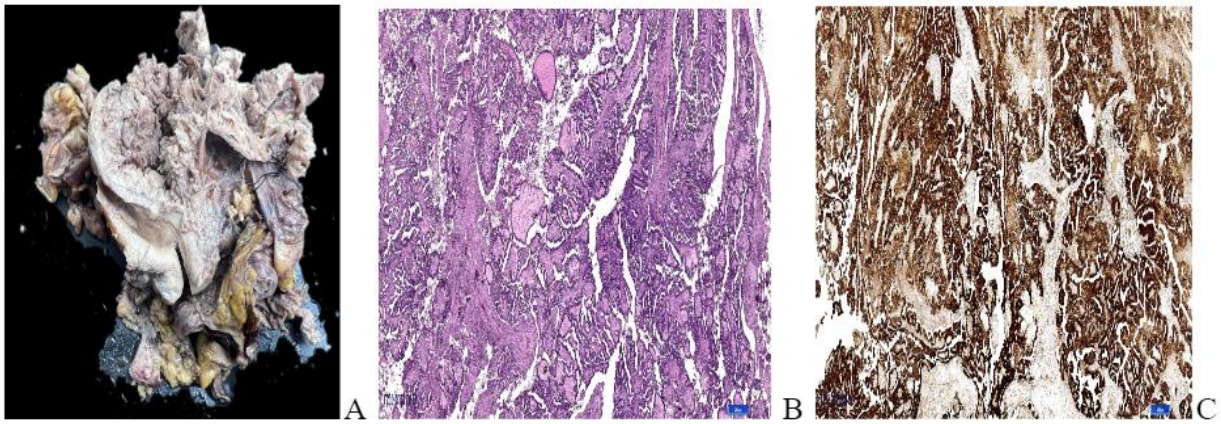


Figure 4



Legends

Fig 1. (a) MRI of pelvis showing a T2 hyperintense lesion near the fundus of the uterus (b), CT of the lung showing randomly distributed air filled cysts present in bilateral lung parenchyma (c), CT of the left kidney showed a heterogeneously enhancing lesion

Fig 2. (a) HPE shows spindle shaped myoid cells, mature adipose tissue and thick walled hyalinized blood vessels(H&E. x100) (b), HPE shows fibrocollagenous tissue infiltrated by tumour cells arranged in sheets and forming vague glandular patterns(H&E. x100)

Fig. 3(a) The lower pole of the left kidney showed a single grey brown to grey yellow, solid and ill defined lesion measuring (b), HPE shows renal parenchyma with a well encapsulated nodular neoplasm composed of spindle cells admixed with mature adipocytes and numerous proliferating blood vessels (H&E. x40) (c), HPE showing angiomyolipoma (H&E. x100) (d), HPE showing mature adipocytes with thick walled blood vessels under high power (H&E. x200) (e), HPE under highest power (H&E. x200) (f) IHC for HMB-45 was positive (IHC. x200)

Fig. 4(a) TAH with BSO specimen shows a large exophytic friable lesion (b), The HPE shows round to oval infiltrating tumour with increased nuclear cytoplasmic ratio and showing hyperchromasia (H&E. x100) (c), IHC for p16 shows positivity (IHC. x200)