

Gastric Adenocarcinoma in Association with Tuberous Sclerosis

Case report

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السرطانة الغدية المعدية المصاحبة للتصلب الحدبي تقرير حالة

أحمد سعيد، منصور المنذري، اكرام برني، سخبال سوهني

المخلص: ندرج هنا أول حالة لسرطان المعدة المصاحب للتصلب الحدبي. والتصلب الحدبي هو اضطراب وراثي جَسَدِيٌّ سائد يمكن أن يتجلى من خلال علامات معقدة مثل الأورام الحميدة في الدماغ وفي بقية الأجهزة الحيوية كالكليتين والقلب والعيون والرئتين والجلد. أما الأعراض فقد تشمل الصرع، التأخر النمائي، المشااكل السلوكية، تشوهات الجلد وأمراض الكلية والرئتين. يحصل التصلب الحدبي نتيجة طفرات في اثنين من المورثات (رقم 1 و2) اللذين يشفران بروتيني الهامارتين والتيوبيرين. اللذان يعملان على كبح جماح نمو الأورام وبذا يتم تنظيم عملية تكاثر الخلايا وتميزها. يصاحب التصلب الحدبي نمو الأورام العابية والأورام الشَّحْمِيَّة العَضَلِيَّة الوَعَائِيَّة. وكذلك سرطان المعدة. يمكن أن تكون هذه مجرد صدفة ولهذا نحتاج إلى تقارير لحالات أخرى.

مفتاح الكلمات: سَرَطَانَةٌ غَدِيَّةٌ مُخَاطِيَّةٌ، الأورام العابية، التصلب الحدبي، أورام عَضَلِيَّةٌ لُفَيَّةٌ وَعَائِيَّةٌ، سرطان المعدة، تقرير حالة، عمان.

ABSTRACT We report the first case of gastric cancer in association with tuberous sclerosis. Tuberous sclerosis is an autosomal dominant disorder which presents with a constellation of signs including benign tumours in the brain and in other vital organs such as the kidneys, heart, eyes, lungs, and skin. A combination of symptoms may include seizures, developmental delay, behavioural problems, skin abnormalities, and lung and kidney disease. It is caused by mutations on either of two genes, tuberous sclerosis genes, TSC1 or TSC2, which encode for the proteins hamartin and tuberin respectively. These proteins act as tumour growth suppressor agents that regulate cell proliferation and differentiation. Tuberous sclerosis has been associated with hamartomatous growths and angiomyolipomas, an association with gastric cancer has not been reported; however, this could be a co-incidental finding and further cases need to be reported.

Keywords: Mucinous adenocarcinoma; Tuberous sclerosis; Hamartoma; Lymphangiomyomatosis; Gastric cancer; Case report; Oman.

WE REPORT THE CASE OF A LADY diagnosed to have gastric adenocarcinoma, who was also known to have tuberous sclerosis. Although, tuberous sclerosis is known to be associated with hamartomatous growths and angiomyolipomas and fibromas, an association with gastric cancer has not been reported previously.

CASE REPORT

A 45 years old Omani lady presented at Sultan Qaboos University Hospital, Muscat, Oman, with a one-week history of marked decrease in appetite and excessive vomiting. Clinical examination showed epigastric fullness, an enlarged palpable hard liver and a Sister Mary Joseph's nodule. These are described as metastatic lesions to the umbilicus from many primary sources (e.g. stomach, pancreas, endometrium, ovary, cervix,



Figure 1: Image of part of face showing *adenoma sebaceum*

colon, small bowel, gallbladder, prostate, lung, and breast). In addition, the left kidney was noted to be enlarged and easily palpable. Examination of her face revealed multiple *adenoma sebaceum* consistent with tuberous sclerosis [Figure 1]. She also had an incidental finding of bilateral corneal opacities, which have not been reported before in association with tuberous sclerosis. Her past medical history was significant for diagnosis of tuberous sclerosis and a right nephrectomy. Initial investigations showed normal haemogram and biochemistry, while a high resolution computed tomography (CT) scan of her lungs showed numerous thin walled cystic air spaces of varying sizes distributed diffusely throughout the lungs with intervening normal lung parenchyma suggestive of lymphangiomyomatosis [Figure 2]. A contrast enhanced CT scan of the abdomen showed the left kidney replaced by a large vascular mass with fat content (arrows) representing an angiomyolipoma [Figure 3]. A non-contrast

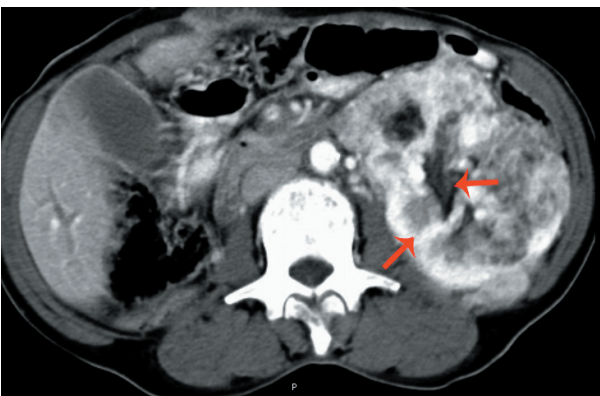


Figure 3: A contrast enhanced computed tomography scan of the abdomen shows the left kidney replaced by a large vascular mass with fat content (arrows) representing an angiomyolipoma

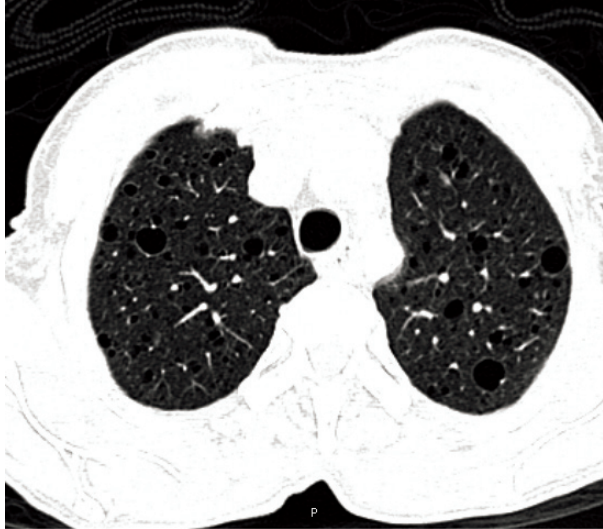


Figure 2: High resolution computed tomography scan of lungs shows bilateral, scattered, thin walled cysts, with intervening normal lung parenchyma

CT brain scan showed a calcified subependymal and left frontal lobe hamartomas (arrows) (Fig 4). In view of obstructive symptoms, she underwent distal palliative gastrectomy. Intra-operative findings showed an antral mass invading into the head of the pancreas. Metastatic disease was also noted in pre-pyloric and portal lymph nodes as well as the peritoneum. The histopathology of postoperative samples showed a moderately differentiated mucin secreting adenocar-

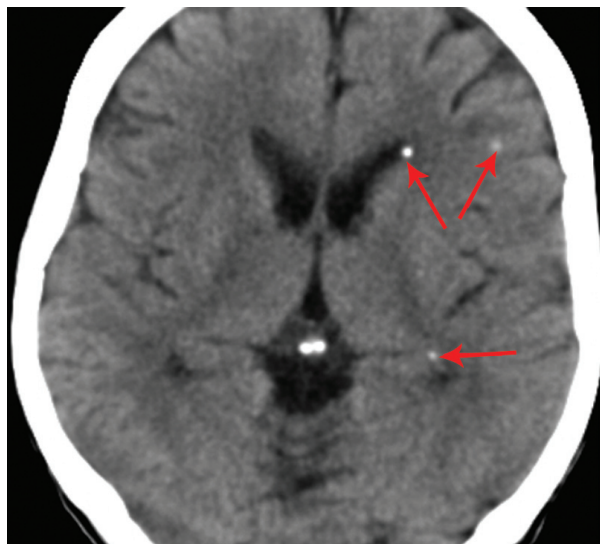


Figure 4: Non contrast computed tomography Scan of brain shows calcified left subependymal hamartomas (arrows) along left lateral ventricle and another one in left frontal lobe with surrounding hypodense white matter suggestive of demyelination

Table 1: Eastern cooperative oncology group (ECOG, Zubrod) performance scale

Performance Status	Description
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all self care, but unable to carry out any work activities. Up and about >50 percent of waking hours
3	Capable of only limited self care; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any self care; totally confined to bed or chair

Oken MM, et al. Am J Clin Oncol 1982; 5:649.

cinoma of the stomach with metastatic deposits in the pre-pyloric and portal lymph nodes as well as the peritoneum.

In summary, this 45 years old lady was found to have Stage IV adenocarcinoma of the stomach, against a background of tuberous sclerosis, and had undergone palliative gastrectomy, with gross macroscopic residual disease. She was subsequently treated with palliative 5-flourouracil by continuous intravenous infusion, she had a partial response. More recently she has developed obstructive jaundice, but still enjoys a World Health Organisation/European clinical oncology group (WHO/ECOG) performance status of 1 [Table 1].

DISCUSSION

Tuberous sclerosis is a genetic disorder with autosomal dominant inheritance.¹ The incidence of tuberous sclerosis is 1 in 6,000 births. Mutations in one of two tumour suppressor genes, tuberous sclerosis complex gene type 1 (TSC₁) and tuberous sclerosis gene type 2 (TSC₂), cause tuberous sclerosis.^{1,2} It is characterised by a tendency to develop tumourous growths in widespread locations throughout the body.^{1,3} Characteristic skin lesions often suggest the diagnosis. Often there is no family history since as many as 60% of cases are due to a new germ line mutation. Usual presentations are either with epilepsy or due to abnormal hamartomatous growths noted incidentally.⁴

The most important hamartomas are cerebral, cortical tubers, which are regions of abnormal cortical architecture with distinctive large neuronal cells. Cortical tubers cause some of the most important clinical manifestations of tuberous sclerosis namely epilepsy, mental retardation, and abnormal behaviour including autism.⁵ Other hamartomatous lesions in tuberous

sclerosis include sub-ependymal nodules, facial angiofibromas, sub-ungual fibromas, forehead plaques, shagreen patches, cardiac rhabdomyomas, and renal angiomyolipomas and cysts.⁶ Pulmonary lymphangiomyomatosis is a rare disease which results from benign proliferation of smooth muscle in lung and other organs.⁷ Cystic lung changes associated with tuberous sclerosis are exceedingly rare occurring in less than 1% of patients.⁸

Genetic predisposition to neoplasia often involves mutations in the tumour suppressors (tuberous sclerosis complex) TSC₁ and TSC₂. Inactivation of TSC₁ and TSC₂ genes contributes to the development of a wide range of hamartomatous lesions. TSC genes play a role in the phosphoinositide 3-kinase pathway, dysregulation of which is implicated in a wide range of human malignancies, raising the possibility that their activation or suppression could contribute to the development of some sporadic cancers such as transitional cell bladder cancer, renal cell cancer and sporadic astrocytomas. Due to improved identification of the variable phenotypic expression, the reported incidence of tuberous sclerosis has increased. Variations in TSC₁ and TSC₂ mutations are related to different phenotypic manifestations and risks of malignancy, such as an increased incidence of the TSC₂ mutation are reported in patients with renal cell carcinoma.

Tuberous sclerosis is well known to be associated with gastric hamartomas; however, association with gastric adenocarcinomas has not yet been reported. Hamartomas are not considered to be a predisposing factor for adenocarcinoma and our case did not show signs of hamartomatous polyps.

CONCLUSION

In conclusion, we report the case of a patient who was diagnosed to have a mucin-secreting adenocarcinoma.

Although hamartomatous polyps have been reported in the stomach in association with familial polyposis coli, a definite association of tuberous sclerosis with stomach cancer is lacking. However, this may be a coincidental finding and needs further reports to establish the association.

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