Gastric Adenocarcinoma in a Patient with Tuberous Sclerosis Complex: A Rare Case Report and Review of Literature

Ramya Ravichandar [1], Rajam Krishna S [2], Priya Sivashankar [3], Sujai Anand [4*]

Abstract

Background: Tuberous sclerosis complex (TSC) is a genetic disorder characterized by benign tumors in multiple organ systems. Caused by mutations in TSC1 or TSC2 genes, TSC primarily leads to benign growths, but rare malignancies have been reported. Malignancies in TSC patients are uncommon, and the association with gastric adenocarcinoma is exceedingly rare. This report presents a case of gastric adenocarcinoma in a 42-year-old male with TSC, highlighting the need for awareness of potential malignancies in TSC patients. Method: The patient, a known case of TSC, presented with swelling in the left axilla, significant weight loss, and reduced appetite. An excision biopsy of the axillary lymph nodes was performed to evaluate the swelling. An upper gastrointestinal (UGI) endoscopy was conducted to identify the primary malignancy source. Results: Histopathological examination of the excised axillary lymph nodes revealed secondary deposits of adenocarcinoma. UGI endoscopy identified multiple polypoidal lesions in the stomach. Biopsy of these lesions confirmed poorly cohesive adenocarcinoma of the signet ring cell type, a subtype of diffuse-type gastric adenocarcinoma. Conclusion: This suggesting the possibility of an under-recognized association. Further studies are needed to explore this potential link, which could impact the surveillance and management of TSC patients, particularly those presenting with atypical symptoms.

Keywords: Tuberous sclerosis complex, Gastric adenocarcinoma, Signet ring cell carcinoma, mTOR pathway, Genetic disorder.

Significance | This case determines a rare co-occurrence of gastric adenocarcinoma in a TSC patient, urging consideration of malignancies in TSC management.

*Correspondence. Sujai Anand , Department of Radiodiagnosis, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
E-mail: Sujai.a@bharathuniv.ac.in

Editor Md Shamsuddin Sultan Khan And accepted by the Editorial Board January 05, 2022 (received for review Nov 29, 2021)

Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder characterized by the growth of benign tumors, known as hamartomas, in multiple organ systems, including the brain, skin, kidneys, heart, and lungs (Crino, Nathanson, & Henske, 2006). It is an autosomal dominant disorder caused by mutations in one of two tumor suppressor genes: TSC1, which encodes the protein hamartin, and TSC2, which encodes the protein tuberin (Jones et al., 1999). These proteins form a complex that negatively regulates the mammalian target of rapamycin (mTOR) pathway, which is crucial for cell growth and proliferation (Rosset, Netto, & Ashton-Prolla, 2017). When either TSC1 or TSC2 is mutated, the mTOR pathway becomes hyperactive, leading to the uncontrolled growth of cells and the formation of various types of tumors and lesions (Gupta et al., 2022). While most tumors associated with TSC are benign, malignant tumors have also been reported, although they are rare (Northrup et al., 2021).

Clinically, TSC presents with a classic triad of features: epilepsy, intellectual disability, and skin abnormalities, such as

Author Affiliation.
[1] Department of Pharmacology, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
[2] Department of Physiology, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
[3] Department of Psychiatry, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
[4] Department of Radiodiagnosis, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India

Please Cite This:
Ramya Ravichandar, Rajam Krishna S, et al. (2022), Gastric Adenocarcinoma in a Patient with Tuberous Sclerosis Complex: A Rare Case Report and Review of Literature, Journal of Angiotherapy, 6(1), 1-5, 2180

hypomelanotic macules (ash-leaf spots), facial angiofibromas, and shagreen patches (Borkowska, Schwartz, Kotulska, & Jozwiak, 2011). The spectrum of manifestations is highly variable, ranging from mild skin lesions to severe neurological impairment (Crino et al., 2006). Most patients with TSC exhibit some degree of neurological involvement, including seizures, which are present in up to 90% of cases (Northrup et al., 2021). The presence of seizures and intellectual disabilities can significantly impact the quality of life for affected individuals (Francis & MacDonald, 2011). Apart from neurological and dermatological features, TSC is also associated with renal angiomyolipomas, cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis (LAM), and subependymal giant cell astrocytomas (SEGAs) (Lendvay & Marshall, 2003).

Despite the well-established association of TSC with benign tumors like hamartomas and angiomyolipomas, reports of TSC patients developing malignancies are uncommon (Sauter et al., 2021). The literature has documented associations between TSC and cancers such as renal cell carcinoma (Gupta et al., 2022), but associations with other malignancies, such as gastric adenocarcinoma, remain exceedingly rare (Ahmed, Burney, Sawhney, & Al-Moundhri, 2009). Gastric adenocarcinoma is a malignant tumor that arises from the glandular epithelium of the stomach lining and is broadly classified into two histological types: intestinal and diffuse (Tatsuta, Okuda, Tamura, & Taniguchi, 1980). While the intestinal type is associated with environmental factors such as diet and Helicobacter pylori infection, the diffuse type has a stronger genetic basis, often involving mutations in the CDH1 gene encoding E-cadherin (Correa, 1992). The occurrence of gastric adenocarcinoma in a patient with TSC poses a unique diagnostic and therapeutic challenge, as it may represent a coincidental finding or suggest a previously unrecognized association (Oh et al., 2011).

In this case report, we describe a 42-year-old male with a known history of TSC who presented with swelling in the axilla. Subsequent investigations, including excision biopsy and upper gastrointestinal endoscopy, revealed poorly cohesive adenocarcinoma of the stomach (Ahmed et al., 2009). To our knowledge, this is one of the few reported cases of TSC associated with gastric adenocarcinoma (Huang & Wang, 2018). This case highlights the need for awareness of potential malignancies in patients with TSC, especially those presenting with unusual symptoms. It also underscores the importance of further studies and case reports to explore any potential association between TSC and gastric adenocarcinoma or other malignancies, which could have significant implications for the management and surveillance of these patients (Sauter et al., 2021).

Case Report

A 42-year-old male with a known history of tuberous sclerosis complex (TSC) presented to the clinic with complaints of swelling in the left axilla for the past two months. The swelling was associated with significant weight loss and reduced appetite. His medical history included epilepsy, for which he was on anti-epileptic medication, and pulmonary tuberculosis, for which he had completed a full course of anti-tuberculous therapy. The patient also had a surgical history of an open appendicectomy several years earlier.

On physical examination, characteristic features of TSC were observed, including adenoma sebaceum on the face. Examination of the left axilla revealed two hard, non-tender, mobile lymph nodes, each approximately 2 cm in size. The rest of the systemic examination was unremarkable.

Given the axillary lymphadenopathy, an excision biopsy of the lymph nodes was performed. Histopathological examination of the excised lymph nodes revealed secondary deposits of adenocarcinoma of the mucinous type, suggesting a metastatic origin. This prompted further investigations to identify the primary site of the malignancy.

An upper gastrointestinal (UGI) endoscopy was performed, which revealed multiple polypoidal lesions with ulceration in the stomach (*Figure 1*). Biopsies of these lesions were taken, and histopathological examination showed poorly cohesive adenocarcinoma of the signet ring cell type, a subtype of diffuse-type gastric adenocarcinoma.

Despite the diagnosis, the patient's clinical condition deteriorated rapidly. He developed worsening symptoms, including cachexia and poor performance status, which prevented any definitive surgical or oncological intervention. The patient ultimately succumbed to the disease shortly after the diagnosis.

This case illustrates a rare presentation of gastric adenocarcinoma in a patient with tuberous sclerosis complex, highlighting the need for awareness of potential malignancies in TSC patients, particularly when presenting with atypical symptoms such as unexplained lymphadenopathy and weight loss.

Discussion

Tuberous sclerosis complex (TSC) is a rare genetic disorder that leads to the formation of hamartomas in multiple organs due to mutations in the TSC1 or TSC2 genes. These genes produce the proteins hamartin and tuberin, respectively, which together inhibit the mammalian target of rapamycin (mTOR) pathway. When either of these genes is mutated, the mTOR pathway becomes overactive, resulting in uncontrolled cell growth and tumor formation. Most tumors associated with TSC are benign, including cortical tubers, subependymal hamartomas, renal angiomyolipomas, cardiac rhabdomyomas, and facial angiofibromas. However, malignant transformation in TSC patients, while rare, has been documented, and there is increasing evidence that these patients might be at risk for developing certain types of malignancies, such as renal cell carcinoma (Borkowska et al., 2011; Gupta et al., 2022).

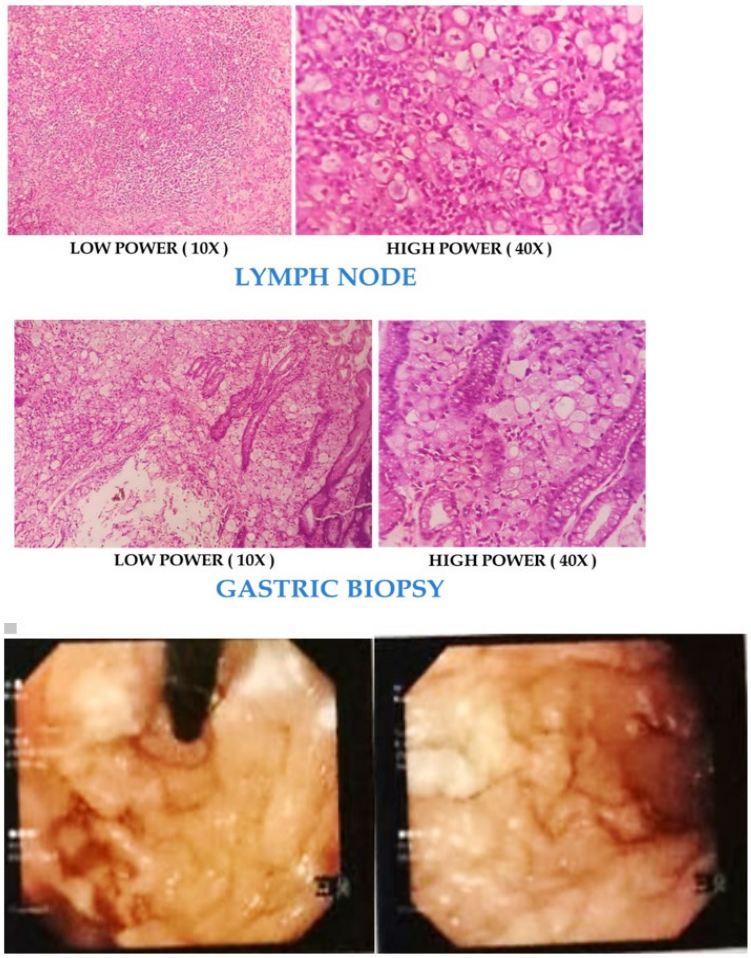

Figure 1. Upper gastrointestinal endoscopy revealed multiple polypoidal lesions with ulcerations in the stomach

Gastric adenocarcinoma, especially the diffuse type characterized by poorly cohesive cells like signet ring cells, is a rare occurrence in TSC patients. This subtype is often associated with mutations in the CDH1 gene, which encodes E-cadherin, rather than with the TSC1 or TSC2 genes (Tatsuta et al., 1980). The present case illustrates a rare presentation of poorly cohesive adenocarcinoma in a 42-year-old male with TSC, who presented with unexplained lymphadenopathy and significant weight loss. The diagnosis was established through an excision biopsy of the axillary lymph nodes, which showed secondary adenocarcinomatous deposits, and an upper gastrointestinal endoscopy, which confirmed a primary gastric origin with signet ring cell morphology (Ahmed et al., 2009). Although the co-occurrence of TSC and gastric adenocarcinoma may represent a coincidental finding, it raises important considerations for clinical practice. There is no established direct association between TSC and gastric adenocarcinoma in the current literature (Crino et al., 2006). However, given the pathogenic loss of tumor suppressor gene function in TSC, it is plausible that the genetic instability could predispose patients to develop secondary malignancies (Dabora et al., 2001). Furthermore, this case emphasizes the importance of vigilance in monitoring TSC patients for atypical symptoms, such as unexplained weight loss or lymphadenopathy, which may indicate an underlying malignancy (Gupta et al., 2022; Habib et al., 2016).

Additionally, while gastric hamartomas are known to occur in adenomatous polyposis coli and rarely in TSC, the de novo development of adenocarcinoma from these polyps, particularly in the absence of adenomatous polyposis coli, is extraordinarily rare (Kim et al., 2000; Oh et al., 2011). This case, therefore, underscores the necessity for further research to explore any potential link between TSC and gastric adenocarcinoma, as well as the need for more case reports to better understand the implications of such an association for clinical management and surveillance (Brook-Carter et al., 1994; Rosset et al., 2017).

Conclusion

This case report highlights a rare presentation of poorly cohesive gastric adenocarcinoma in a patient with tuberous sclerosis complex (TSC). While there is no established link between TSC and gastric adenocarcinoma, this case suggests the need for heightened awareness among clinicians regarding the potential for

Author contributions

R.R., R.K.S., P.S., and S.A. supervised the study, contributed to data analysis, and collaboratively drafted and revised the manuscript.

Acknowledgment

The authors were thankful to their department.

Competing financial interests

The authors have no conflict of interest.

References

Ahmed, S., Burney, I., Sawhney, S., & Al-Moundhri, M. S. (2009). Gastric adenocarcinoma in association with tuberous sclerosis: Case report. Sultan Qaboos University Medical Journal, 9(1), 75-78.

Borkowska, J., Schwartz, R. A., Kotulska, K., & Jozwiak, S. (2011). Tuberous sclerosis complex: Tumors and tumorigenesis. International Journal of Dermatology, 50(1), 13–20. https://doi.org/10.1111/j.1365-4632.2010.04600.x

Brook-Carter, P. T., Peral, B., Ward, C. J., Thompson, P., Hughes, J., Maheshwar, M. M., ... & Harris, P. C. (1994). Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease—a contiguous gene syndrome. Nature Genetics, 8(4), 328–332. https://doi.org/10.1038/ng1094-328

Crino, P. B., Nathanson, K. L., & Henske, E. P. (2006). The tuberous sclerosis complex. New England Journal of Medicine, 355(13), 1345–1356. https://doi.org/10.1056/NEJMra055160

Dabora, S. L., Jozwiak, S., Franz, D. N., Roberts, P. S., Nieto, A., Chung, J., ... & Thiele, E. A. (2001). Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. American Journal of Human Genetics, 68(1), 64–80. https://doi.org/10.1086/316969

Ekong, R. (n.d.). The TSC1 gene homepage: Global Variome. Retrieved from https://databases.lovd.nl/shared/genes/TSC1

Ekong, R. (n.d.). The TSC2 gene homepage: Global Variome. Retrieved from https://databases.lovd.nl/shared/genes/TSC2

Eledrisi, M. S., Stuart, C. A., & Alshanti, M. (2002). Insulinoma in a patient with tuberous sclerosis: Is there an association? Endocrine Practice, 8(2), 109–112. https://doi.org/10.4158/EP.8.2.109

Gupta, S., Kang, H. C., Faria, S. C., Choyke, P. L., & Kundra, V. (2022). Tuberous sclerosis complex (TSC): Renal and extrarenal imaging. Academic Radiology, 29(3), 439–449. https://doi.org/10.1016/j.acra.2021.08.014

Gupta, S., Stanton, M. L., Reynolds, J. P., Whaley, R. D., Herrera-Hernandez, L., Jimenez, R. E., ... & Marzban, S. S. (2022). Lessons from histopathologic examination of nephrectomy specimens in patients with tuberous sclerosis complex: Cysts, angiomyolipomas, and renal cell carcinoma. Human Pathology, 129, 123–139. https://doi.org/10.1016/j.humpath.2022.06.009

Habib, S. L., Al-Obaidi, N. Y., Nowacki, M., Pietkun, K., Zegarska, B., Kloskowski, T., ... & Rej, P. (2016). Is mTOR inhibitor good enough for treatment all tumors in TSC patients? Journal of Cancer, 7(12), 1621–1631. https://doi.org/10.7150/jca.16978

Jones, A. C., Shyamsundar, M. M., Thomas, M. W., Maynard, J., Idziaszczyk, S., Tomkins, S., ... & Evans, J. (1999). Comprehensive mutation analysis of TSC1 and TSC2—and phenotypic correlations in 150 families with tuberous sclerosis. American Journal of Human Genetics, 64(5), 1305–1315. https://doi.org/10.1086/302520

Kim, B. K., Kim, Y. I., & Kim, W. H. (2000). Hamartomatous gastric polyposis in a patient with tuberous sclerosis. Journal of Korean Medical Science, 15(4), 467-470. https://doi.org/10.3346/jkms.2000.15.4.467

Lendvay, T. S., & Marshall, F. F. (2003). The tuberous sclerosis complex and its highly variable manifestations. The Journal of Urology, 169(5), 1635-1642. https://doi.org/10.1097/01.ju.0000058253.40352.60

Northrup, H., Aronow, M. E., Bebin, E. M., Bissler, J., Darling, T. N., de Vries, P. J., ... & Thiele, E. A. (2021). Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatric Neurology, 123, 50–66. https://doi.org/10.1016/j.pediatrneurol.2021.04.001

Northrup, H., Koenig, M. K., Pearson, D. A., & Au, K. S. (1993). Tuberous sclerosis complex. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. Stephens, & A. Amemiya (Eds.), GeneReviews. Seattle (WA): University of Washington.

Oh, S. J., Oh, C. A., Kim, D. H., Choi, M. G., Noh, J. H., Sohn, T. S., ... & Kim, S. (2011). Adenocarcinoma derived from gastric hamartomatous polyps. Journal of the Korean Surgical Society, 81(6), 419-422. https://doi.org/10.4174/jkss.2011.81.6.419

Orosz, P., Kollák, Z., Pethő, Á., Fogarasi, A., Reusz, G., Hadzsiev, K., ... & Róka, R. (2023). The importance of genetic testing in the differential diagnosis of atypical TSC2-PKD1 contiguous gene syndrome-case series. Children, 10(3), 420. https://doi.org/10.3390/children10030420

Rosset, C., Netto, C. B. O., & Ashton-Prolla, P. (2017). TSC1 and TSC2 gene mutations and their implications for treatment in tuberous sclerosis complex: A review. Genetics and Molecular Biology, 40(1), 69–79. https://doi.org/10.1590/1678-4685-GMB-2016-0204

Sauter, M., Belousova, E., Benedik, M. P., Carter, T., Cottin, V., Curatolo, P., ... & Kwiatkowski, D. J. (2021). Rare manifestations and malignancies in tuberous sclerosis complex: Findings from the TuberOus SClerosis registry to increase disease awareness (TOSCA). Orphanet Journal of Rare Diseases, 16(1), 301. https://doi.org/10.1186/s13023-021-01880-6

Tatsuta, M., Okuda, S., Tamura, H., & Taniguchi, H. (1980). Gastric hamartomatous polyps in the absence of familial polyposis coli. Cancer, 45(4), 818-823. https://doi.org/10.1002/1097-0142(19800215)45:4<818::AID-CNCR2820450435>3.0.CO;2-5