

**ADENOCARCINOMA OF THE STOMACH IN ASSOCIATION WITH TUBEROUS
SCLEROSIS- A CASE REPORT****Dr. Bijoya Debnath*¹ and Dr. Hemalatha Ganapathy²**Final Year Postgraduate¹, Professor & HOD²
Department of Pathology, SBMCH, Chennai, Tamil Nadu.***Corresponding Author: Dr. Bijoya Debnath**

Final Year Postgraduate, Department of Pathology, SBMCH, Chennai, Tamil Nadu.

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ABSTRACT

Tuberous sclerosis is an autosomal dominant syndrome occurring at a frequency of approximately 1 in 6000 births. It is characterized by the development of hamartomas and benign neoplasms involving the brain and other vital organs such as the kidneys, heart, eyes, lungs, and skin. The most frequent clinical manifestations are seizures, autism, and mental retardation. One tuberous sclerosis locus (TSC1) is found on chromosome 9q34, and encodes a protein known as hamartin; the more commonly mutated tuberous sclerosis locus (TSC2) is at 16p13.3 and encodes tuberin. These two proteins associate to form a complex that inhibits the kinase mTOR, which is a key regulator of protein synthesis and other aspects of anabolic metabolism. Tuberous sclerosis has been associated with hamartomatous growths and angiomyolipomas, an association with gastric adenocarcinoma has been reported only once as a co-incident finding and our case in the second finding.

KEYWORDS: Adenocarcinoma stomach, Tuberous sclerosis, Lymph node, Gastric cancer, Signet ring.

We report the case of a male diagnosed to have poorly cohesive adenocarcinoma of stomach- signet ring cell type, who was also known to have tuberous sclerosis on medication for epilepsy. Although, tuberous sclerosis is known to be associated with hamartomatous growths and angiomyolipomas and fibromas, an association with gastric cancer has been reported only once previously and ours is the second case.

INTRODUCTION

A 42-year-old male, known case of Tuberous Sclerosis, on treatment for epilepsy, presented with two months history of swelling of the left upper limb. On examination, edema was noted over the left upper limb and 2 nodes were noted in the central group of axilla, each measuring 2 x 2 cm, which was mobile and non tender. Excision biopsy was done for the node and sent for histopathological evaluation where we received 2 grey-white, irregular, fibro-fatty masses. The larger mass measured 3 x 2.5 x 1.5 cm, nodular with fibro-fatty areas. On cut section greasy and focal yellowish area were noted. The smaller mass measured 1 x 1 x 0.5 cm and was homogenous, grey-tan on cut section. The histopathology showed fatty tissue with lymphocytes, fibrous tissue, vascular proliferation and groups of vacuolated cells with polymorphous nuclei. Thick walled blood vessels with invasion and tumour emboli were seen along with lymph node replaced by aggregates of signet ring type of cell, large vacuolated cells and

vascular proliferation. PAS showed positivity in most of vacuolated cells thus giving the impression of secondary adenocarcinomatous deposits – mucinous type. The probable primary being gastrointestinal tract or respiratory system. Further work up was done on which endoscopy revealed multiple polypoidal lesions throughout the stomach, associated with inflammation and ulceration. Hence endoscopy guided biopsy was taken from the polypoid gastric lesions and sent to us for histopathological evaluation. Grossly we received multiple, grey-white, soft tissue fragments, measuring < 0.5 cc in aggregates which was all embedded. The microscopy showed fragments of distorted mucosa & numerous islands of mucin-laden malignant cells with moderate nuclear anaplasia with PAS positivity in all vacuolated cells thus confirming poorly cohesive adenocarcinoma of the stomach – signet ring cell type with metastatic deposits in the axillary lymph nodes.

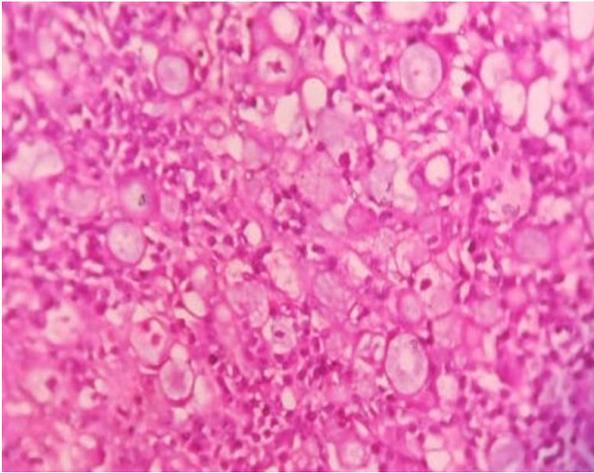


Fig. 1: (L/P) Picture showing lymphoid follicle infiltrated by vacuolated cells.

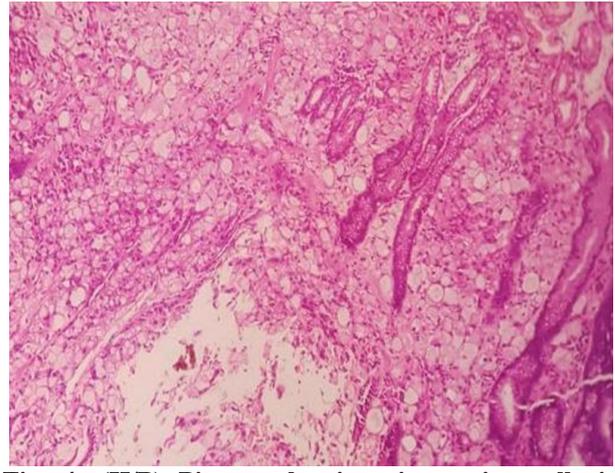


Fig. 4: (H/P) Picture showing signet ring cells in between gastric glands.

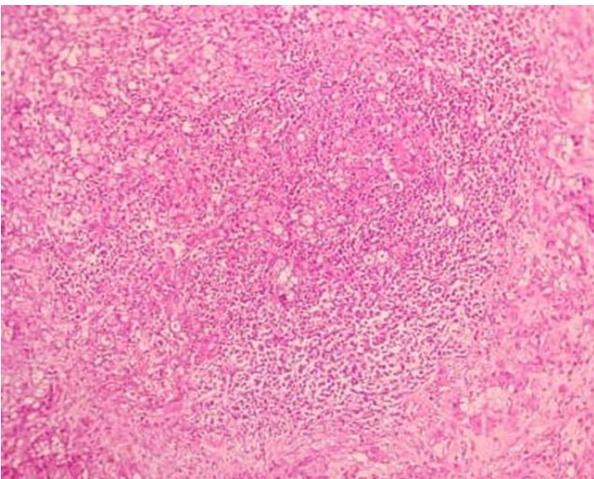


Fig. 2: (H/P) Picture showing mucin filled vacuolated cells- signet ring cell.

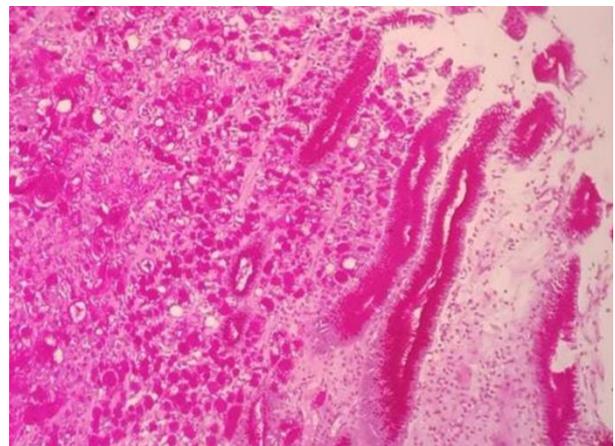


Fig. 5: (L/P) Picture showing PAS positivity in the gastric glands and mucin.

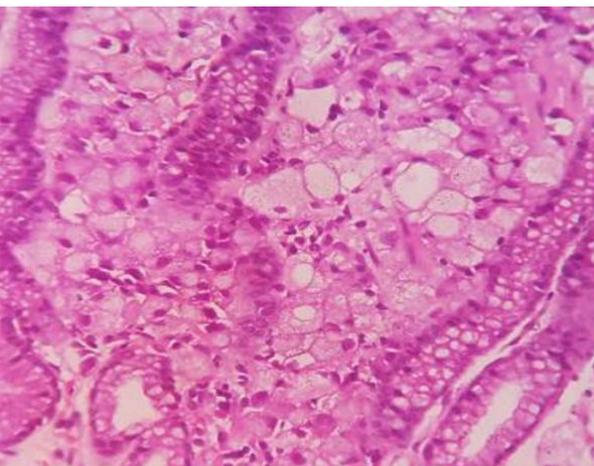


Fig. 3: (L/P) Picture showing gastric glands with numerous mucin laden malignant cells.

DISCUSSION

Adenocarcinoma is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers.^[1] It is often separated morphologically into intestinal type, which tends to form bulky masses, and a diffuse type, which infiltrates the wall diffusely, thickens it, and is typically composed of signet ring cells.^[2,3] Early symptoms of both types of gastric adenocarcinoma resemble those of chronic gastritis,^[4] and peptic ulcer disease, including dyspepsia, dysphagia, and nausea.

Poorly cohesive gastric adenocarcinoma is also called linitis plastica / diffuse type / signet ring cell adenocarcinoma.^[5] It presents as an infiltrative growth of poorly differentiated discohesive malignant cells. It is more common in the young with mean age of presentation at 48 years with equal predilection for man and women. Rarely hereditary diffuse gastric cancer, autosomal dominant is related to mutations in E-cadherin gene (CDH1). Germline truncating mutations of the E-cadherin (CDH1) gene have been found in families with hereditary diffuse gastric cancer.^[6] This molecular alteration, which results in decreased or loss of expression of E-cadherin, a component of the adherens

junctions, explains the discohesive,^[7] growth of diffuse-type gastric carcinoma.^[8]

The gross alterations usually begin in the pre-pyloric area with broad region of gastric wall or entire stomach is extensively infiltrated by malignancy. It shows thickened, rigid, leather bottle-like stomach hence termed linitis plastica. Pyloric obstruction often develops as the wall of the stomach becomes thickened and rigid.^[9] The muscle is hypertrophic and segmented by the presence of thin, parallel, grayish white, longitudinal lines that give it a comb-like appearance. Microscopically diffuse growth of malignant cells is seen, associated with extensive fibrosis and inflammation often with entire wall is involvement.^[10] Glandular formations are rare, and most tumor cells grow individually or in linear arrays. Most of the mucin produced is intra-cytoplasmic, resulting in the typical signet ring appearance (mucin pushes nucleus to periphery).^[11] Pools of extracellular mucin may also be present, but as long as signet ring cells are evident, this tumor should be categorized as signet ring adenocarcinoma rather than mucinous adenocarcinoma.^[12]

Tuberous sclerosis is a genetic disorder with autosomal dominant inheritance¹³. 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. There is a tendency to develop tumour growths in widespread locations throughout the body.^[14] Usual presentations are either with epilepsy or due to abnormal hamartomatous growths noted incidentally.^[15] It is well known to be associated with gastric hamartomas however, association with gastric adenocarcinomas has been reported only once. 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 Poorly cohesive adenocarcinoma of stomach- signet ring cell type. 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 as only one such case has been reported so far. However, with our case being the second incidental finding, there lies the needs for further reports to establish the association.

REFERENCES

1. Robbins and Cotran pathologic basis of disease, tenth edition.
2. Gore R. Gastrointestinal cancer. *Radiol Clin North Am*, 1997; 35: 295–310.
3. Lauren T. The two histological main types of gastric carcinoma. *Acta Pathol Microbiol Scand*, 1965; 64: 34.
4. Kwon KJ, Shim KN, Song EM, Choi JY, Kim SE, Jung HK, Jung SA. Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the stomach. *Gastric Cancer*, 2014; 17: 43–53.
5. Lauwers G, Carneiro F, Graham D, et al. *Classification of Tumours of the Digestive System*. 4th ed Lyon: IARC Press, 2010; 48–58.
6. Humar B, Blair V, Charlton A, et al. E-cadherin deficiency initiates gastric signet-ring cell carcinoma in mice and man. *Cancer Res.*, 2009; 69: 2050–6.
7. Humar B, Guilford P. Hereditary diffuse gastric cancer: a manifestation of lost cell polarity. *Cancer Sci.*, 2009; 100: 1151–1157.
8. Hyung WJ, Noh SH, Lee JH, et al. Early gastric carcinoma with signet ring cell histology. *Cancer*, 2002; 94: 78–83.
9. 17. Kim DY, Park YK, Joo JK, et al. Clinicopathological characteristics of signet ring cell carcinoma of the stomach. *ANZ J Surg.*, 2004; 74: 1060–1064.
10. Kwon K-J, Shim K-N, Song E-M, et al. Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the stomach. *Gastric Cancer*, 2014; 17: 43–53.
11. Kawamura H, Kondo Y, Osawa S, et al. A clinicopathologic study of mucinous adenocarcinoma of the stomach. *Gastric Cancer*, 2001; 4: 83–86.
12. Chu PG, Chung L, Weiss LM, Lau SK. Determining the site of origin of mucinous adenocarcinoma: an immunohistochemical study of 175 cases. *Am J Surg Pathol*, 2011; (35): 1830–1836.
13. Knowles MA, Hornigold N, Pitt E. Tuberous sclerosis complex (TSC) gene involvement in sporadic tumours. *Biochemical Soc Trans*, 2003; 31: 597–602.
14. Carsillo T, Astrinidis A, Henske EP. Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangiomyomatosis. *Proc Natl Acad Sci USA*, 2000; 91: 11413–16.
15. Parry L, Maynard JH, Patel A, Hodges AK, von Deimling A, Sampson JR, et al. Molecular analysis of the TSC1 and TSC2 tumour suppressor genes in sporadic glial and glioneuronal tumours. *Hum Genet*, 2000; 107: 350–6.