

Paraneoplastic Focal Segmental Glomerulosclerosis Associated With Gastrointestinal Stromal Tumors With Cutaneous Metastasis: a Case Report

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Case Report

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Abstract

Background: Gastrointestinal stromal tumor (GIST) is one of most common mesenchymal neoplasms occurring in different areas of the gastrointestinal tract. GISTs with cutaneous metastasis is very rare and its rarity cutaneous GISTs have not been well characterized. Focal segmental glomerulosclerosis (FSGS) is also rare among paraneoplastic nephritic syndromes (PNS).

Case presentation: In this case report, we described a 64-year-old patient with cutaneous metastasis GIST accompanied by nephrotic syndrome as PNS, in whom symptomatic treatment was ineffective, but clinical remission was achieved after surgery. Moreover, the patient has a missense mutation of *NPHP4*. *NPHP4* served as a negative regulator of the Hippo pathway. Hippo signaling pathway is involved in the development and progression of FSGS. *NPHP4* is also indeed a driving force for proliferation in tumor cells. Therefore, the mutation of *NPHP4* in this patient could explain the occurrence of GIST and FSGS and this was therefore not a random association.

Conclusions: This is the first reported case of a GIST with cutaneous metastasis accompanied by nephrotic syndrome as PNS.

Background

Gastrointestinal stromal tumor (GIST) is one of most common mesenchymal neoplasms occurring in different areas of the gastrointestinal tract. The most frequent site of GISTs occurs in stomach (60%), followed by the small bowel (35%) and colon rectum (< 5%) [1]. Immunohistochemistry would be helpful for the diagnosis because GISTs show immunoreactivity for CD117 (95%), CD34 (70%) and DOG-1, a complementary stain of CD117 [2]. GISTs are usually benign with a malignant transformation rate of 10–30%. With regard to metastatic GISTs, DeMatteo's group [3] has previously reviewed 200 cases and reported that 61% of the metastases showed liver involvement, 20% had intraabdominal involvement and 6% had bone involvement. Since 2002, 10 cases of a cutaneous metastasis from GISTs have been described and one report estimated these occurrences to represent 1% of advanced GISTs [4].

Paraneoplastic syndrome (PNS) is a disorder or symptom caused by cancer or a reaction to tumors, but does not result from the local presence of cancer cells [5]. The signs and symptoms of PNS are diverse, but there are common features in PNS, including neuropathy, skin disease, and nephrotic syndrome.

In this case report, we describe a patient with cutaneous metastatic GIST accompanied by nephrotic syndrome as PNS, in whom symptomatic treatment was ineffective but clinical remission was achieved after surgery. To the best of our knowledge, this is the first time to present a unique case of cutaneous metastasis GIST accompanied by FSGS as PNS.

Case Presentation

A 64-year-old Chinese man was admitted to our hospital complaining of edema of the face and lower limbs for more than four months. Laboratory examinations revealed severe proteinuria (3.77 g/24 h;

normal range, 0–0.15 g/24 h), hypoalbuminemia (1.8 g/dL), and hyperlipidemia (cholesterol 15.7 mmol, triglyceride 3.34 mmol/L) and increased serum creatinine level (152 µmol; normal range, 44–133 µmol). These clinical parameters suggested that it was the nephrotic syndrome. A kidney biopsy was performed and the results showed that there were nine glomeruli, including one glomerulosclerosis and one segmental glomerulosclerosis with peripheral podocytosis, vascuole and granular degeneration in the renal tubular epithelial cells (Fig. 1a, b). These pathological findings suggested that it was considered to be the focal segmental glomerulosclerosis (FSGS), not the otherwise specified (NOS). The immunohistochemistry of the kidney revealed that CD117 (Fig. 1c) is positive in the proximal tubule cells and CD34 (Fig. 1d) is positive in the glomerular capillary loop, peritubular capillary and arterioles, but DOG-1 was negative. Physical examination revealed multiple nodules and lumps with a smooth surface that could be seen throughout the body (Fig. 1e). Enlargement of the cervical, axillary and inguinal lymph nodes was observed obviously. Fat degeneration and necrosis were observed in lymph node and no tumor metastasis was revealed (Fig. 1f). H&E staining of the skin showed spindle cell tumor-like hyperplasia, which was slightly heteromorphic with focal necrosis and rarely mitotic (Fig. 1g). Immunohistochemistry staining revealed that the tumor cells were positive for CD34, Bcl-2, CD99, Ki67 and vimentin, but negative for smooth muscle actin (SMA) and S-100. Immunohistochemistry staining of CD34 was shown as representativeness (Fig. 1h). The diagnosis was a desmoid tumor (DT) basing on the above detection results.

Then, gastroscopy was performed and the results showed that a 0.6 cm mucosal bulge that was hard to the touch, and poor mobility could be seen on the greater curvature of the stomach (Fig. 2a). Many 0.4–2 cm bulges can be seen in the anterior wall of the middle and upper of the gastric fundus with fractured surface and fresh blood (Fig. 2b). Moreover, pathologic examination revealed the destruction of the gastric solid membrane structure and spindle cell tumor-like hyperplasia with mild dysplasia (Fig. 2c) and epithelioid cells are occasionally seen with 6–8 mitotic figures/50 HPF (Fig. 2d). By immunohistochemistry staining, CD117 (Fig. 2e), CD34 (Fig. 2f) and SMA were positive, DOG1 was probable positive, and S-100 and CK were negative. These findings supported the diagnosis of GISTs. In addition, a heterozygous missense mutation was found in *NPHP4* gene of the subject (NPHP4: NM_015102: exon17: c.2198G > A: p.G733D), could explain the occurrence of GIST and FSGS and this was therefore not a random association. Partial gastrectomy was performed. 102–105 Cyclosporine was used in the outpatient setting for three days, and the patient's feelings of discomfort stopped. Despite of receiving prednisone acetate 50 mg QD for three months, the patient's severe proteinuria and hypoalbuminemia did not improve. Additional immunohistochemistry of the skin revealed that CD117 (Fig. 2g) and DOG1 (Fig. 2h), the two most sensitive and specific markers for diagnosis of GIST [6] were positive. Finally, the diagnosis was a metastatic cutaneous GIST. Two weeks after removing the tumor by operation, the patient's serum albumin and urinary protein levels improved remarkably (Fig. 3).

Discussion And Conclusions

GISTs arise from the interstitial cells of Cajal, which serve as a pacemaker for the gastrointestinal tract by creating slow wave potentials that direct smooth muscle to contract. GISTs primarily metastasize to the

liver and peritoneum, while cutaneous metastases are the least common. While, the mechanism of GISTs metastasis to the skin remains unknown. It is hypothesized that the presence may indicate the multiple internal metastases [3]. It was misdiagnosed as DT at the beginning until the recognition of skin metastasis of GISTs by detecting the expression of CD117, CD34 and DOG1 in skin. It should also be advised for patients with a history of GISTs to have a full skin exam to detect any visible clues of the status of metastatic tumor burden.

In our case, the patient had a missense mutation of *NPHP4*. *NPHP4* locates on chromosome 1p36 and encodes a protein called nephrocystin-4/nephroretinin [7]. Nephrocystin-4 colocalises and interacts with nephrocystin 1,3 and inversin in primary cilia and associated appendages, adherens junctions, and focal adhesions [8]. Individuals with mutations in *NPHP4* most frequently have an associated with the nephronophthisis [9]. Some data identify that *NPHP4* served as a negative regulator of the Hippo pathway [10]. In acute renal injury, Hippo signaling pathway may be involved in the apoptosis of tubule epithelial cells, epithelial-mesenchymal transition and acute renal injury progress to chronic kidney disease and other processes [11]. In addition, Hippo signaling pathway is also involved in the development and progression of a variety of chronic kidney disease, including FSGS, diabetic nephropathy, polycystic kidney disease [12]. The conserved Hippo signaling pathway regulates organ size in *Drosophila melanogaster* and mammals and plays an essential role in tumor suppression and the cell proliferation [13]. *NPHP4* is indeed a driving force for proliferation in tumor cells. Therefore, the mutation of *NPHP4* in this study could explain the occurrence of GIST and FSGS and this was therefore not a random association.

Our patient had a cutaneous metastatic GIST, and needed to be differentiated from Gardner's syndrome, an autosomal hereditary disease with multiple adenomatous polyps in colorectal and some extracolonic lesions. It is characterized by multiple adenomatous polyps in the colorectal region with osteoma, soft-tissue tumor, and tooth abnormality. In addition, 30–75% of patients with Gardner's syndrome also have dental abnormalities [14]. Osteomas is a necessary diagnosis of Gardner's syndrome. Its molecular genetic basis is the mutation of the *APC* in 5q21. Unfortunately, this patient did not undergo colonoscopy. However, based on the absence of an *APC* mutation, family history, and the fact that the patient had no osteoma or dental abnormalities, the etiology can be differentiated the Gardner's syndrome.

Theoretically, the diagnosis of paraneoplastic glomerulopathy should rely on three strong criteria. Firstly, a clinical and histologic remission occurs after complete surgical removal of the tumor or chemotherapy-induced complete remission of the disease. In this case, symptomatic treatment was ineffective but clinical remission was achieved after surgery. So, the nephrotic syndrome can be diagnosed as PNS. Secondly, a renal relapse accompanies recurrence of the neoplasia. In other words, proteinuria should directly correlate with tumor activity. Thirdly, a pathophysiologic link is established between the two diseases, including the detection of tumor antigens and antitumor antibodies within subepithelial immune deposits [15]. In our case, the immunohistochemistry on the kidney revealed positive for CD117 and CD34, but negative for DOG-1. Telocytes (TCs) were indicated as a distinctive cell type by after being previously described as "Interstitial Cajal-Like Cells" [16]. Qi reported TCs in the interstitium of the human

kidney cortex. Renal TCs were found to express CD34 and CD117 with variable intensity [17]. Therefore, the positive CD34 and CD117 in the kidney were not significant. Nephrotic syndrome can occur as malignancy-associated PNS, and previous studies have estimated that cancer occurs in 11–22% of patients with nephrotic syndrome [5]. The most common pathological type of tumor-associated nephropathy is membranous nephropathy (44–49%). FSGS is extremely rare among PNS and it has been reported that FSGS can be seen in renal cell carcinoma, invasive thymoma, and lung cancer [18]. There has been only one case of GIST of the stomach that was associated with nephrotic syndrome as PNS. Nephrotic syndrome improved after surgery in 78% of patients [5]. Considering cancer is a potential cause of nephrotic syndrome, surgical resection should be performed in the presence of PNS condition. In our case, the patient's proteinuria and hypoalbuminemia did not respond to symptomatic treatment. After tumor removal, the clinical remission of nephrotic syndrome was immediately achieved. Thus, FSGS can be considered a GIST-associated PNS. However, the variant of FSGS that has been reported in PNS was the collapsing variant, due to the overexpression of vascular endothelial growth factor, which leads to collapsing FSGS. This was not FSGS NOS.

Some studies have proven that α -actinin-4 mutations play an important role in the development of PNS [19]. Unfortunately, this patient did not have any *ACTN4* mutations. However, these hypotheses seem insufficient to explain the case of GIST accompanied by FSGS as PNS. Tyrosine kinase inhibitors (TKIs) are effective in GISTs, but reports have focused on TKIs-associated renal injury leading to FSGS. In the future, we will use cytotoxic chemotherapy for this patient under intensive follow-up. GISTs are currently regarded as potentially malignant tumors. Discrimination of a benign GISTs from a malignant GIST is by postoperative histological analysis (tumor diameter, mitotic index, whether the tumor has metastasized and Ki67 expression level) [20]. According to the cutaneous metastasis GIST, this case is a high-risk patient with poor prognosis. Joensuu's group recommended for high-risk patients shorter imaging intervals of about 3–4 months during the time period of approximately two years following discontinuation of imatinib [21]. Our patient risk of recurrence would be reduced based on the follow-up schedules.

In conclusion, FSGS caused by cutaneous metastasis GIST is quite rare, and to the best of our knowledge, this is the first time to report such a case. The *NPHP4* mutation in this case can explain the occurrence GISTs and FSGS. It was not a random association.

Abbreviations

ACTN4: α -Actinin-4; APC: adenomatous polyposis coli; CTNNB1: β -Catenin gen 1; DT: desmoid tumor; FSGS: Focal segmental glomerulosclerosis; GIST: gastrointestinal stromal tumor; PNS: paraneoplastic nephritic syndromes; TCs: Telocytes; TKIs: Tyrosine kinase inhibitors.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient. A copy of the consent form is available for review and can be provided on request. This Case Report was done in adherence to the CARE Guidelines.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Author's contributions

Jun Zhou wrote the manuscript and conducted the literature review. Zhen Yang, Cuishun Yang and Hua Lin participated in the clinical care of the patient. Wanqiong Yuan participated in paper submitting and revising. All authors assisted the results interpretation and manuscript revision. All authors read and approved the final manuscript.

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References

1. Vassos N, Agaimy A, Hohenberger W, Croner RS. Coexistence of gastrointestinal stromal tumors (GIST) and malignant neoplasms of different origin: prognostic implications. *J Surg*. 2014.12(5):371-7.
2. Phan M, Jones S, Jenkins J, Pant S, Khawandanah M. Pancreatic GIST in a patient with limited stage small cell lung cancer: a case report and review of published cases. *Case Rep Oncol Med*. 2016.2016:9604982.
3. Kim YJ, LeeW J, Won CH, Choi JH, Lee MW. Metastatic cutaneous duodenal gastrointestinal stromal tumor: a possible clue to multiple metastases. *Ann Dermatol*. 2018. Jun;30(3):345-347.
4. Aickara DJ, McBride J, Morrison B, Romanelli P. Multidrug resistant gastrointestinal stromal tumor with multiple metastasis to the skin and subcutaneous soft tissue: A case report and review of

- literature. *J Cutan Pathol.* 2020.Apr;47(4):398-401.
5. Takane K, Midorikawa Y, Yamazaki S, Kajiwara T, Yoshida N, Kusumi Y, Takayama. Gastrointestinal stromal tumor with nephrotic syndrome as a paraneoplastic syndrome: a case report. *Med Case Rep.* 2014;27:8.
 6. Novelli M, Rossi S, Rodriguez-Justo M, Taniere P, Seddon B, Toffolatti L, Sartor, C, et al. DOG1 and CD117 are the antibodies of choice in the diagnosis of gastrointestinal stromal. *Histopathology.* 2010 Aug;57(2):259-70.
 7. Remi Salomon, Sophie Saunier, Patric Niaudet. Nephronophthisis. *Pediatr Nephrol.*2009,24(12):2333-44.
 8. Marion Delous, Nathan E. Hellman, Helori-Mael Gaude, et al. Nephrocystin-1 and nephrocystin-4 are required for epithelial morphogenesis and associate with PALS1/PATJ and Par6. *Human Molecular Genetics,* 2009,18(24):4711-4723.
 9. Simms, Ann Marie Hynes, Lorraine Eley, et al. Nephronophthisis: a genetically diverse ciliopathy. *Int J Nephrol,* 2011,527137.
 10. Sandra Habbig, Malte P, Bartram, Roman U. Muller et al. NPHP4, a cilia-associated protein, negatively regulates the Hippo pathway. *J Cell Biol,*2011,193(4)633-42.
 11. Zhao S, Yin J, Zhou L, et al. Hippo/mst1 signaling mediates microglial activation following acute cerebral ischemia-reperfusion injury[J]. *Brain Behav Immun,* 2016,17(6):1503-1520.
 12. Kirtida Mistry, MBBCh, DCH, MRCPCH, et al. Novel mutations in NPHP4 in a consanguineous family with histological findings of focal segmental glomerulosclerosis. *Am J Kidney Dis,* 2007,50(5):855-864.
 13. Zanconato F, Piccolo S. Eradicating tumor drug resistance at its YAP-biomechanical roots. *EMBO J,* 2016, 35(5):459-461.
 14. Seehra J, Patel S, Bryant C. Gardner's syndrome revisited clinical case and overview of the literature. *Orthod.* 2016, Mar;43(1):59-64.
 15. Ronco PM. Paraneoplastic glomerulopathies: new insights into an old entity[J]. *Kidney Int,* 1999,56(1):355-377.
 16. L M Popescu, Maria-Simonetta Fausson-Pellegrini. TELOCYTES-a case of serendipity: the winding way from Intersititial Cells of Cajal (ICC), via Ineterstitial Cajal-Like Cells (ICLC) to TELOCYTES. *J Cell Mol Med.* 2010 Aprl;14(4):729-40.
 17. Qi G, Lin M, Xu M, Manole CG, Wang X, Zhu T. *J Cell Mol Med.* 2012 Dec;16(12):3116-22.
 18. Jeyabalan A, Geara AS, Frey Nv, Palmer MD, Hoqan JJ. Paraneoplastic focal segmental glomerulosclerosis associated with acute lymphocytic leukemia. *Kidney Int Rep.* 2019. Jun;4(10):1494-1498.
 19. Meng L, Cao S, Lin N, Zhao J, Cai X, Liang Y, Huang K, et al. Identification of a novel ACTN4 gene mutation which is resistant to primary nephrotic syndrome therapy. *BioMed Res Int.* 2019 Dec;14:5949485.

20. Akahoshi K, Oya M, Koga T, Shiratsuchi Y. Current clinical management of gastrointestinal stromal tumor. *World J Gastroenterol.* 2018 Jul;24(26):2806-2817.
21. Joensuu J, Martin-Broto J, Nishida T, Reichardt P, Schoffski P, Maki RG. Follow-up strategies for patients with gastrointestinal stromal tumour treated with or without adjuvant imatinib after surgery. *Eur J Cancer.* 2015 Aug;51(12):1611-7.

Figures

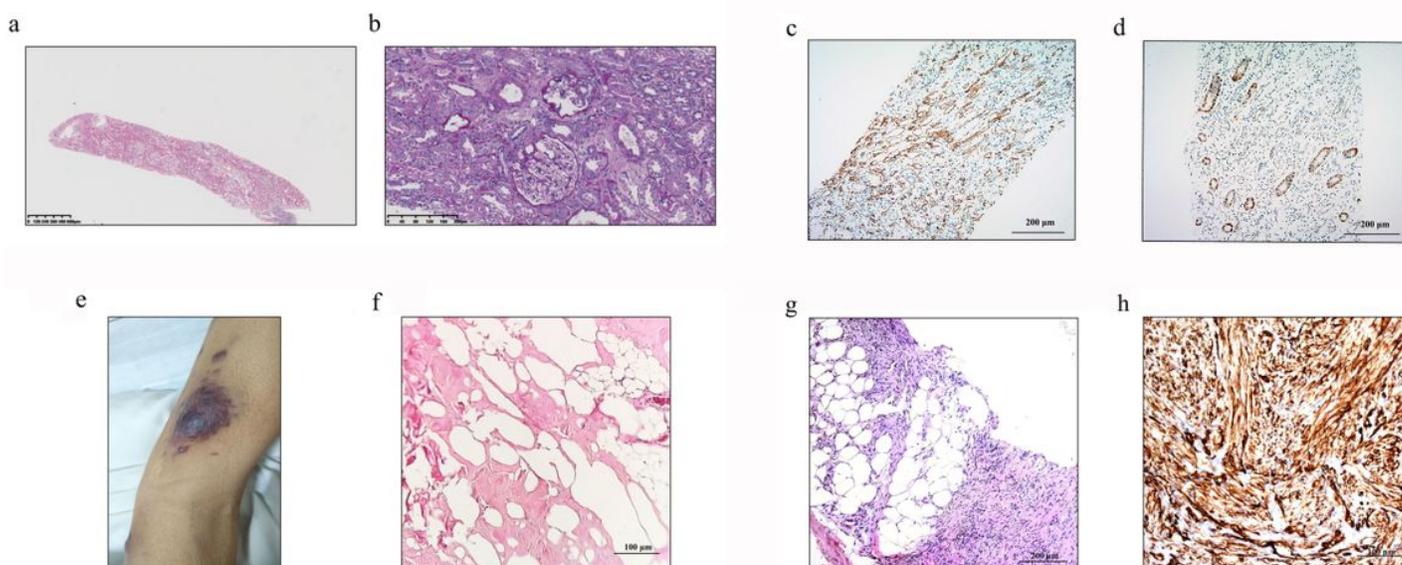


Figure 1

Histological features of the kidney biopsy and dermatological manifestation. (a). HE staining of kidney biopsy. (b). Periodic acid-silver methenamine staining of kidney. (c). Representative immunohistochemical staining for expression of CD34 in the kidney. (d). Representative immunohistochemical staining for expression of CD117 in the kidney. (e). Infiltrative plaques scattered throughout the body. (f). H&E staining of lymph node. (g). H&E staining of the skin. (h). Representative immunohistochemical staining for expression of CD34.

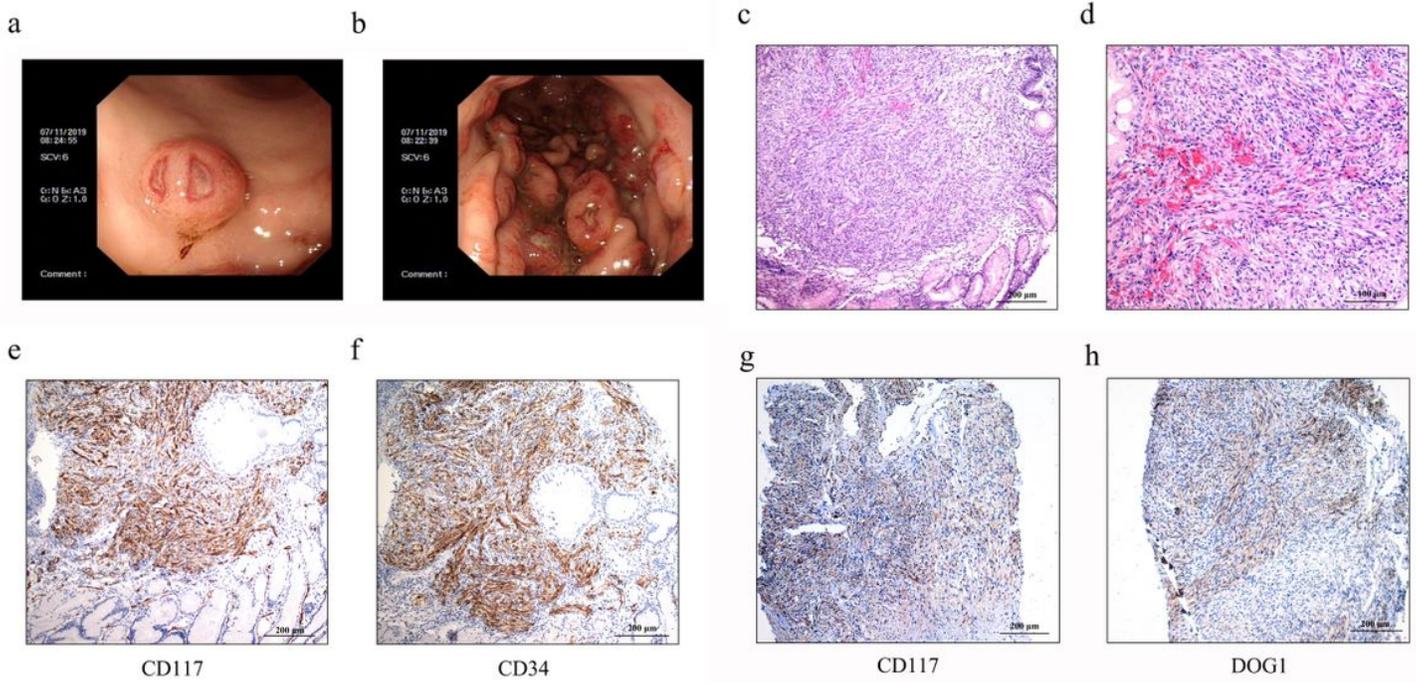


Figure 2

The findings of the gastroscopy and pathological findings of the tumors. (a). Representative photomicrograph taken by gastroscopy with a diameter of 0.6 cm mucosal bulge on the greater curvature of the stomach. (b). Representative photomicrograph taken by gastroscopy with 0.4-2 cm bulges in the anterior wall of the middle and upper part of the gastric fundus. (c). H&E staining of the muscular layer of the gastric wall is composed of spindle cells. (d). H&E staining of Epithelioid cells are occasionally seen with 6-8 mitotic figures/50 HPF. (e). Representative immunohistochemical staining for expression of CD117 in the stomach. (f). Representative immunohistochemical staining for expression of CD34 in the stomach. (g). Representative immunohistochemical staining for expression of CD117 in skin. (h). Representative immunohistochemical staining for expression of DOG1 in skin.

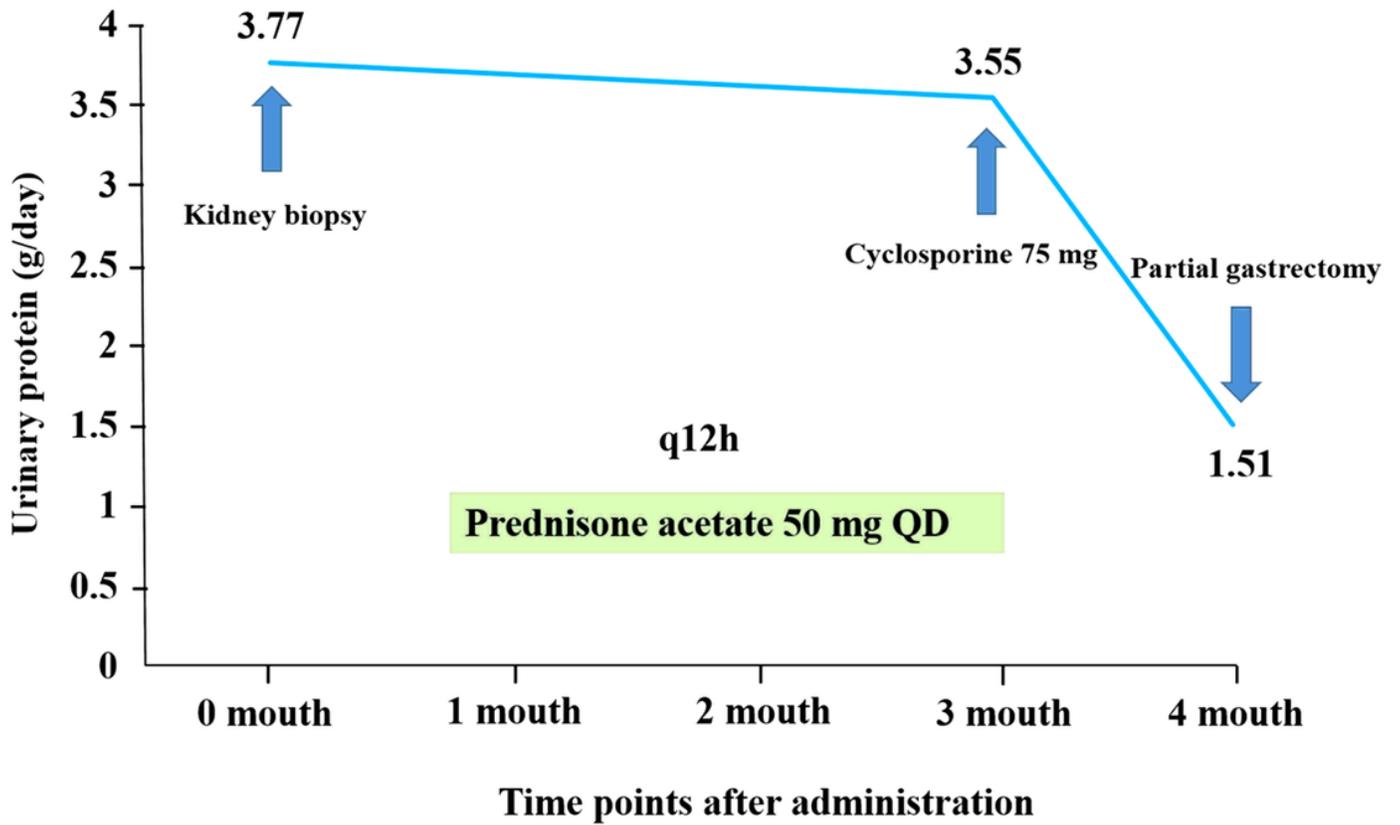


Figure 3

The patient's clinical course. A graph of the urine protein levels post the administration.

Supplementary Files

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