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Minimal Change Nephrotic Syndrome Associated with Gefitinib and a Successful Switch to Erlotinib

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Abstract

Minimal change nephrotic syndrome (MCNS) is a common form of nephrotic syndrome (NS). We herein present the case of a 57-year-old woman with advanced lung adenocarcinoma treated with the tyrosine kinase inhibitor (TKI) gefitinib who developed NS. A renal biopsy revealed minor glomerular abnormalities, and the patient's symptoms improved exclusively with the discontinuation of gefitinib. Therefore, we diagnosed her with MCNS associated with gefitinib treatment. A few months later, however, she developed recurrent lung tumors. Following the challenging initiation of the TKI erlotinib, she achieved remission without proteinuria. We thus conclude that erlotinib is a potential treatment option in patients with NS associated with gefitinib therapy.

Key words: gefitinib, erlotinib, nephrotic syndrome, adverse effect

Introduction

Minimal change nephrotic syndrome (MCNS) is a common form of nephrotic syndrome (NS). Most cases of MCNS are idiopathic, although various drugs, neoplasms, infections and atopic attacks have been reported to be associated with its onset (1). Numerous agents may cause drug-induced NS, primarily including non-steroid anti-inflammatory drugs (NSAIDs) and antimicrobials (1). In contrast, gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, rarely causes drug-induced NS, with only one case having been previously reported (2).

We herein present the case of a 57-year-old woman with advanced lung adenocarcinoma treated with gefitinib who developed NS. A renal biopsy revealed minor glomerular abnormalities, and the patient's symptoms improved exclusively with the discontinuation of gefitinib. A few months later, however, computed tomography (CT) revealed new pulmonary nodules, which were thought to be derived from the recurrence of cancer. The patient subsequently received erlotinib as the next-line therapy and achieved remission, without proteinuria. In this report, we present the clinical course of our patient, the details of which suggest the usefulness of alternative indications for erlotinib therapy in patients with MCNS associated with gefitinib treatment.

Case Report

The patient was a 57-year-old woman with no history of smoking. She had received a diagnosis of a right lung adenocarcinoma at 48 years of age and consequently underwent lobectomy of the right lower lung with mediastinal lymph node resection. The pathological stage was pT1N0M0; therefore, no additional treatment was required. As no recurrence was detected five years after the surgery, follow-up was

discontinued.

A chest X-ray obtained at 56 years of age revealed no abnormalities; however, the patient experienced dyspnea six months later, which did not improve. She therefore visited our hospital, and a chest X-ray showed right pleural effusion. Further examinations, including cytological assessments of the pleural effusion and CT scanning, revealed a lung adenocarcinoma with an EGFR exon 19 deletion, with a pathological stage of T4N0M1a. The tumor was considered to be inoperable, and the patient was prescribed the tyrosine kinase inhibitor gefitinib (250 mg/day). The pleural effusion disappeared immediately after treatment, and gefitinib was assumed to have been effective at that time.

Six months later, the patient suddenly developed edema of the lower limbs in addition to weight gain and again visited our hospital. The laboratory data showed hypoalbuminemia, hyperlipidemia and heavy proteinuria, findings strongly suggestive of NS. Although gefitinib had achieved a pathologically complete response to the lung adenocarcinoma, the drug was strongly suspected to be the cause of the NS. The dose of gefitinib was therefore discontinued, and the patient was admitted to our hospital for a further examination.

On admission, the patient was found to have a blood pressure of 106/43 mmHg and pulse of 61 beats/min with a regular rhythm. Edema of the lower limbs was evident; however, the neurological findings were unremarkable. Meanwhile, a chest X-ray demonstrated clear lung fields (Fig. 1), the findings of electrocardiography were normal and the results of 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) were negative. The laboratory data were as follows: blood urea nitrogen (BUN), 13.3 mg/dL; serum creatinine, 0.61 mg/dL; serum total protein (TP), 4.5 g/dL; serum albumin (Alb), 1.8 g/dL; serum total cholesterol, 297 mg/dL; and

carcinoembryonic antigen (CEA), 4.8 ng/mL. The 24-hour urine protein excretion was 8.3 g/day, and the selectivity index was 0.17. Based on these findings, we made a diagnosis of NS and subsequently performed a renal biopsy. Of the 34 glomeruli examined via light microscopy, two were globally sclerosed. The remaining 32 glomeruli exhibited a slight increase in the mesangial matrix, although no increases in the number of mesangial cells were observed (Fig. 2a). Partially mild tubular atrophy and fibrosis were noted in the interstitium. Immunofluorescence microscopy did not reveal any glomerular deposits of complement or immunoglobulins, whereas electron microscopy showed minor glomerular abnormalities with partial foot process effacement (Fig. 2b). Therefore, we diagnosed the patient with MCNS.

Following the discontinuation of gefitinib, the patient's proteinuria gradually decreased, without the administration of corticosteroids. Two months later, the TP and Alb levels were 6.7 g/dL and 4.0 g/dL, respectively, and the degree of proteinuria was within the normal range, indicating complete remission. Finally, we confirmed the diagnosis of MCNS associated with gefitinib treatment. A few months after the discontinuation of gefitinib, however, CT revealed two new nodular lesions near the right pleura, which suggested the recurrence of cancer (Fig. 3). Following a detailed explanation of the potential adverse effects, the patient provided her informed consent for treatment with another tyrosine kinase inhibitor, erlotinib (100 mg/day). Fortunately, a follow-up CT scan obtained two months after the initiation of erlotinib revealed the disappearance of the nodular lesions. The patient subsequently achieved a pathological complete response with respect to the lung cancer, without proteinuria, i.e., there was no evidence of recurrence of NS (Fig. 4).

Discussion

We herein reported the case of a patient with MCNS associated with gefitinib treatment in which the administration of erlotinib was successful in treating recurrent lung cancer without causing proteinuria. Most cases of MCNS are idiopathic, although various drugs, neoplasms, infections and atopic attacks have been reported to be associated with its onset (1). Therefore, it is important to obtain an accurate differential diagnosis for selecting subsequent treatment. Regarding the differential diagnosis in this case, we first excluded the possibility of infection or atopic attacks, as the patient exhibited neither signs or symptoms nor other findings suggestive of these diseases. We next considered the potential for other neoplasms, since hematologic malignancies, such as Hodgkin lymphoma, non-Hodgkin lymphoma and leukemia, may be associated with MCNS (3). Although there are a few case reports suggesting a relationship between MCNS and lung cancer (4-6), the present patient's laboratory data and CT and FDG-PET findings did not reveal any malignancies, except for the lung adenocarcinoma noted at the onset of NS. While we cannot completely exclude the possibility of idiopathic MCNS, our patient achieved complete remission two months after the discontinuation of gefitinib, which is a much shorter time period than that usually observed for spontaneous remission in cases of idiopathic MCNS (7). Additionally, based on the fact that the NS improved exclusively following the discontinuation of gefitinib and the patient did not develop NS after receiving erlotinib as the next-line therapy for the recurrent lung cancer, we diagnosed her condition as MCNS associated with the administration of gefitinib.

Gefitinib is an EGFR tyrosine kinase inhibitor (8) that is reportedly effective in patients with tumors containing EGFR mutations (9, 10). The most common adverse effects of gefitinib treatment are rashes, diarrhea, acne, dry skin, nausea and vomiting. Although gefitinib-related interstitial lung disease is a well-known serious

side effect that may result in death (11), most adverse effects of this drug are mild-to-moderate in nature and do not require the discontinuation of therapy (12). To date, adverse renal effects have been reported in only a few cases (2, 13, 14). Kumasaka et al. (2) first reported a case of MCNS associated with gefitinib treatment. In that case, NS developed four months after the initiation of gefitinib therapy, suggesting that the occurrence of NS associated with gefitinib is a late-onset adverse effect, as noted in our case. Furthermore, Wan et al. (13) reported a case of acute kidney injury associated with gefitinib therapy. In both of these prior cases, as seen in our patient, only the discontinuation of treatment improved the NS and renal dysfunction.

Erlotinib is another widely used EGFR tyrosine kinase inhibitor. One retrospective study found no significant differences between erlotinib and gefitinib in terms of progression-free survival, although more adverse events were reported in the erlotinib-treated group, including rashes, anorexia and constipation (15). Adverse renal events are extremely rare in patients undergoing erlotinib treatment, including only one case report of double antineutrophil cytoplasmic autoantibody (ANCA)-negative pauci-immune crescentic glomerulonephritis (16). In contrast, no cases of NS associated with erlotinib have been reported to date. On the other hand, interestingly, animal experiments have shown that erlotinib reportedly attenuates proteinuria and inhibits the development of diabetic nephropathy (17). Therefore, the effects of erlotinib treatment on the kidneys are currently under investigation.

The present case raises the important question as to why erlotinib does not cause NS, although its mechanism of action is similar to that of gefitinib, in terms of its function as an EGFR tyrosine kinase inhibitor. One possible explanation for this phenomenon is that the cause of drug-induced NS is related to drug hypersensitivity

reactions. Mihovilovic et al. (18) reported a patient with repeated episodes of NS induced by NSAIDs, including diclofenac and meloxicam, in which the administration of celecoxib, a cyclooxygenase (COX)-2 selective NSAID, interestingly did not induce the onset of NS, suggesting that a difference in chemical structure between these drugs may play a role in hypersensitivity reactions. Similarly, the difference in the chemical structures of gefitinib and erlotinib may explain the differences in the reactions in the kidneys to these two drugs. The effects of the long-term use of erlotinib on the kidneys remain unknown; therefore, further careful monitoring is required in the current case.

In conclusion, clinicians should consider the possibility of MCNS associated with gefitinib treatment in NS patients receiving gefitinib therapy. Erlotinib is a potential treatment option in patients with MCNS associated with the administration of gefitinib. However, further studies are needed to clarify various aspects of the associated pathophysiology.

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Figure legends

Figure 1

Chest X-ray obtained on admission showing no abnormalities.

Figure 2

Renal biopsy findings. **(a)** A slight increase in the mesangial matrix was observed without an increase in the number of mesangial cells (periodic acid-Schiff staining, ×400). **(b)** Minor glomerular abnormalities with partial foot process effacement (arrow) (×2,500).

Figure 3

Computed tomography performed after the discontinuation of gefitinib showing two new nodular lesions near the right pleura (arrows).

Figure 4

Clinical course. U-pro: urinary protein, g/gCr: urinary protein/creatinine ratio

Fig. 1

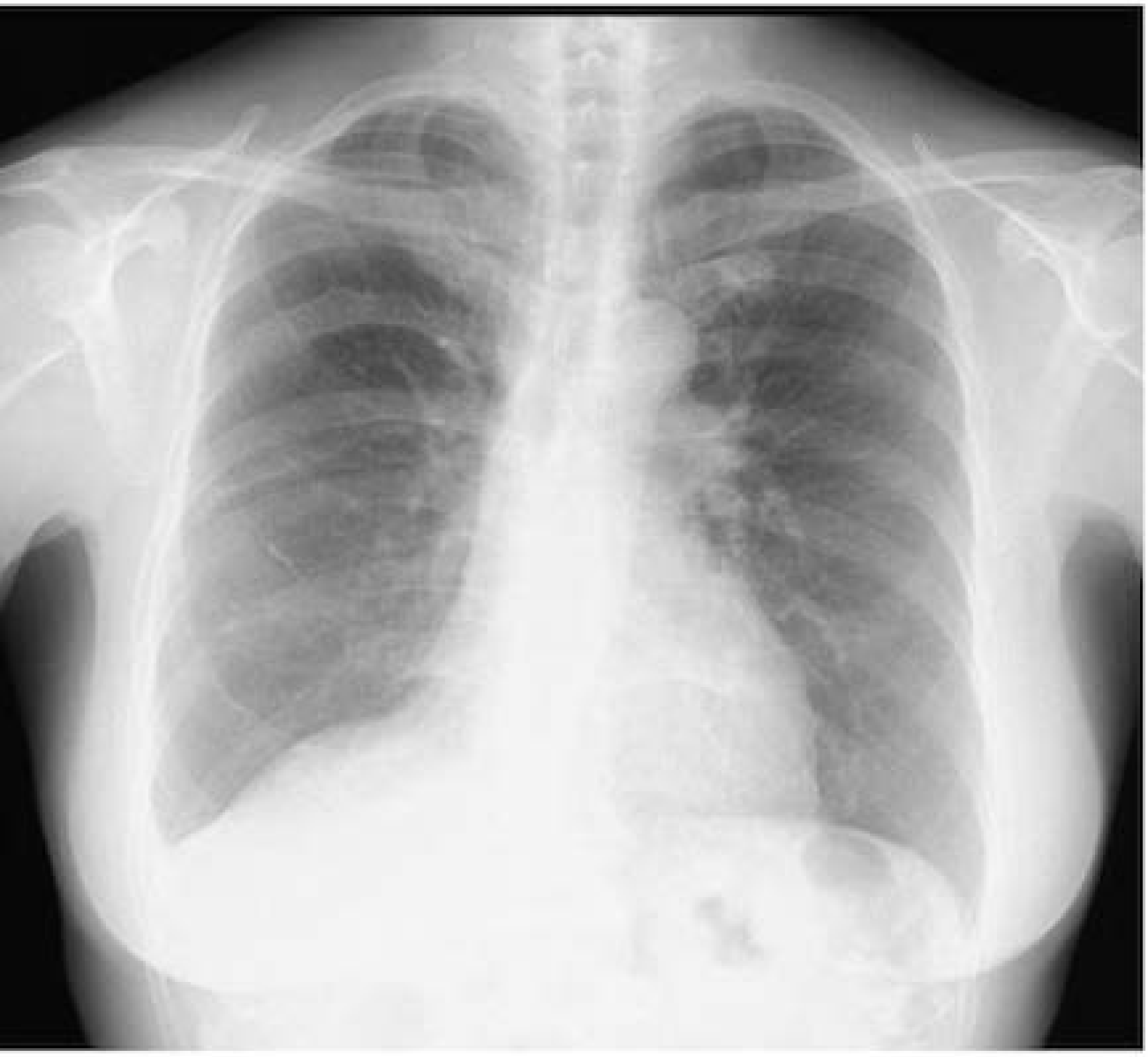

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Fig. 2b

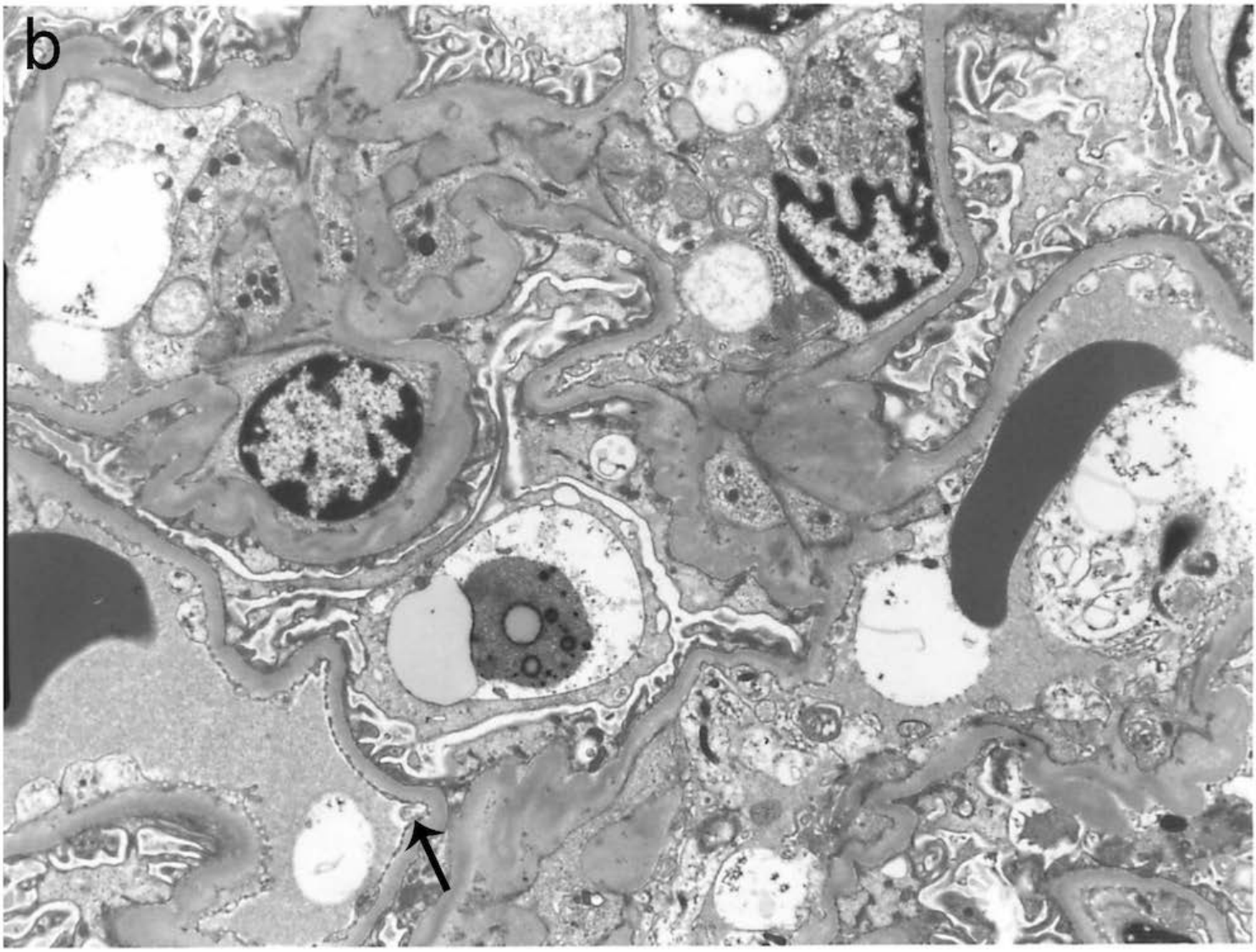

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Fig. 2a

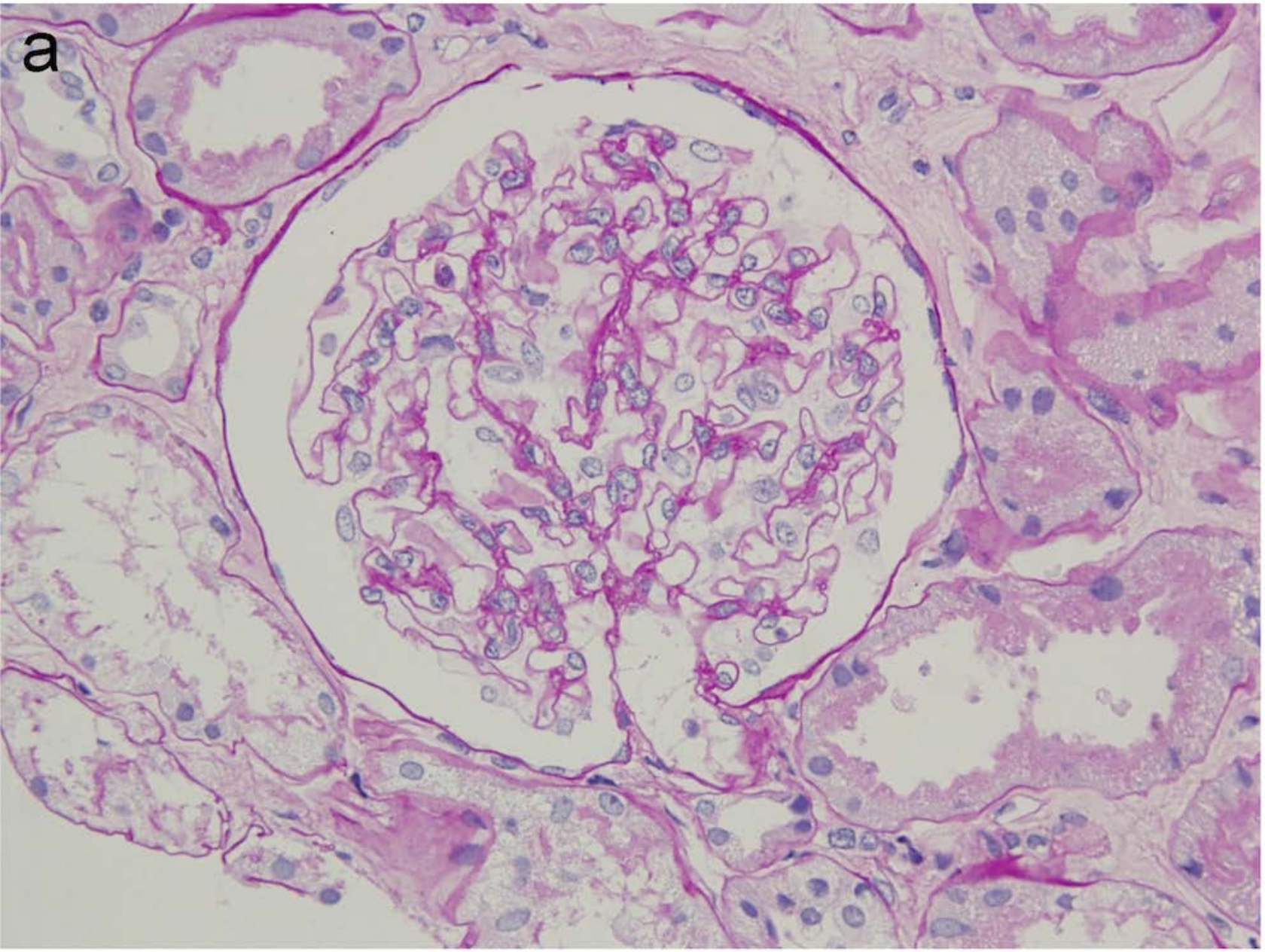

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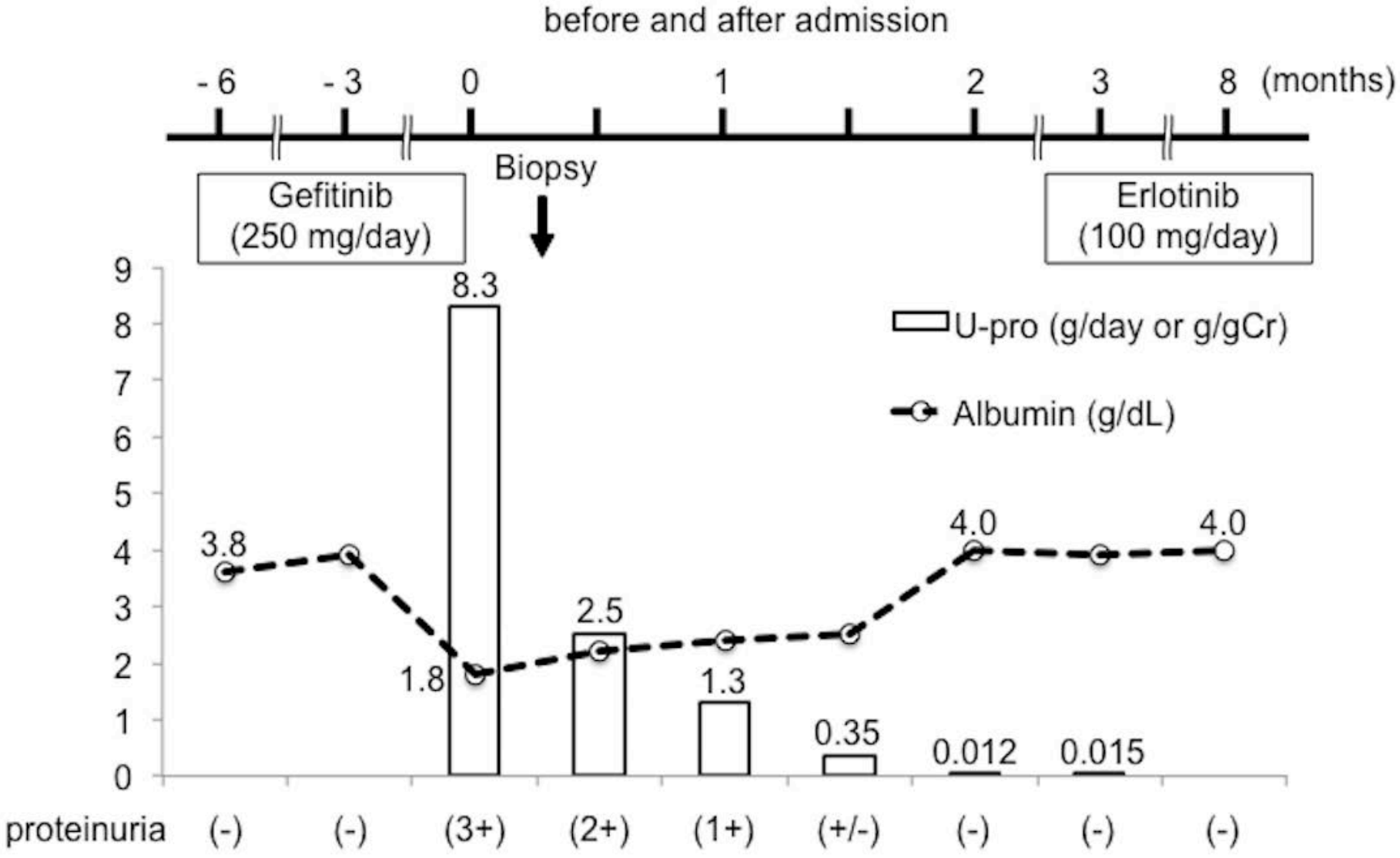
Fig. 4



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