Recurrent paraneoplastic nephrotic syndrome: insights from a Lynch syndrome patient with multiple malignancies

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SHORT COMMUNICATION

Recurrent paraneoplastic nephrotic syndrome; insights from a Lynch syndrome patient with multiple malignancies

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Abstract

Nephrotic syndrome is a common clinical presentation of glomerulopathy. A glomerulopathy as a paraneoplastic manifestation caused by underlying malignancy is rare. In patients with a solid tumor, membranous nephropathy is the most frequent paraneoplastic glomerulopathy. We present a case of recurrent paraneoplastic nephrotic syndrome caused by minimal change disease in a patient with Lynch syndrome. Over the years, a decrease in creatinine clearance and nephrotic-range proteinuria repeatedly functioned as a warning signal for underlying malignancies; consecutively, a colon adenocarcinoma, renal cell carcinoma and gastric adenocarcinoma were diagnosed. After treatment of the malignancies the nephrotic syndrome resolved without immunosuppressive therapy. Our patient also developed a primary lung carcinoma thrice, which did not cause an exacerbation of the minimal change disease. To further elucidate the mechanism behind the development of this phenomenon, we performed immunohistochemical analysis for vascular endothelial growth factor (VEGF) on the different tumor specimens. We found a high VEGF expression in the gastro-intestinal tumors, whereas the VEGF expression in the lung tumors was low, suggesting an association between VEGF expression and the development of paraneoplastic minimal change disease. This case report not only underlines the importance of considering a malignancy as a cause for (recurrent) nephrotic syndrome, especially in patients with an increased risk of developing malignancies like Lynch syndrome patients, but also suggests a role for VEGF in the pathogenesis of paraneoplastic minimal change disease.

Keywords Paraneoplastic · Nephrotic syndrome · Minimal change disease · VEGF · Lynch syndrome

Introduction

Nephrotic syndrome is a clinical syndrome characterized by edema, heavy proteinuria (more than 3.5 g/24 hours) and hypoalbuminemia [1]. It is a common clinical presentation of a glomerulopathy such as focal segmental glomerulosclerosis, membranous nephropathy or minimal change disease. Minimal change disease is characterized by alterations of glomerular epithelial cells seen by electron microscopy, a normal appearance of a kidney biopsy on light microscopy and absence of immune deposits on immunofluorescent study [2–4].

We present a case of recurrent paraneoplastic minimal change disease associated with different solid malignant tumors in a patient with Lynch syndrome, an autosomal dominantly inherited cancer susceptibility syndrome caused by a pathogenic germline variant in one of the mismatch repair genes [5]. This patient also had three lung tumors

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which did not cause a relapse of the nephrotic syndrome, which offered a unique opportunity to further investigate the pathophysiological mechanism of paraneoplastic minimal change disease.

Case report

A 42-year-old man underwent a colonoscopy in June 2012 because of a change in bowel habits. He had been diagnosed with diffuse cutaneous systemic sclerosis seven years earlier and in 2009 a T1 cutaneous squamous cell carcinoma was removed. His family history was positive for renal carcinoma (father), cervical cancer and a large cell carcinoma of the bile duct (mother) and esophageal cancer (maternal grandfather), but negative for colorectal cancer. Colonoscopy showed an obstructive colon cancer that could not be passed by the colonoscope. Based on the scope length inserted, the estimated tumor location was the ascending colon. Biopsies confirmed the presence of an adenocarcinoma, showing a weak expression of MLH1/PMS2. An extended right hemicolectomy was performed in July 2012 (Fig. 1 point A). Surprisingly the resection specimen showed no tumor but only an adenoma with a diameter of 2.8 cm with high grade dysplasia and weak MLH1/PMS2 expression without *MLH1* hypermethylation. The patient was referred for further analysis to the clinical genetics department were the diagnosis of Lynch syndrome was confirmed by the finding of a pathogenic germline variant (c.112 A > C, p.Asn38His) in exon 1 of the *MLH1* gene.

One month after colorectal surgery he developed edema in both legs, proteinuria of 8 g/24 hours, a decrease in creatinine clearance with an eGFR MDRD of 20 ml/min/1,73m2 and hypoalbuminemia of 25 g/L. He was diagnosed with nephrotic syndrome and was treated with an angiotensin-converting enzyme inhibitor (enalapril) and loop diuretics (furosemide) in combination with a fluid restriction. During treatment the nephrotic syndrome initially improved. A paraneoplastic syndrome was considered and a kidney biopsy was taken. This kidney biopsy showed 23 glomeruli, 2 with global glomerulosclerosis (which was considered consistent with normal ageing). The glomeruli showed reactive changes of podocytes and parietal epithelial cells and focal congestion of capillary tufts, but without segmental adhesions or thrombosis. There was no significant interstitial fibrosis or tubular atrophy and the vasculature was normal. Immunofluorescence was negative and electron microscopy showed damage and global effacement of the podocytes, altogether leading to a diagnosis of minimal change disease.

Few days after the kidney biopsy result was available, the patient presented to the emergency department with a bowel obstruction caused by a tumor in the splenic flexure. In hindsight, this was probably the tumor that had been diagnosed at the initial colonoscopy, but had not been removed by the extended right hemicolectomy. A left hemicolectomy was performed (Fig. 1 point B) and the resection specimen showed a T4aN0 adenocarcinoma in the splenic flexure. In the perioperative period, proteinuria levels had risen again to the nephrotic range, with a peak of 11 g/24 hours a few weeks after surgery. In the months after the resection of the

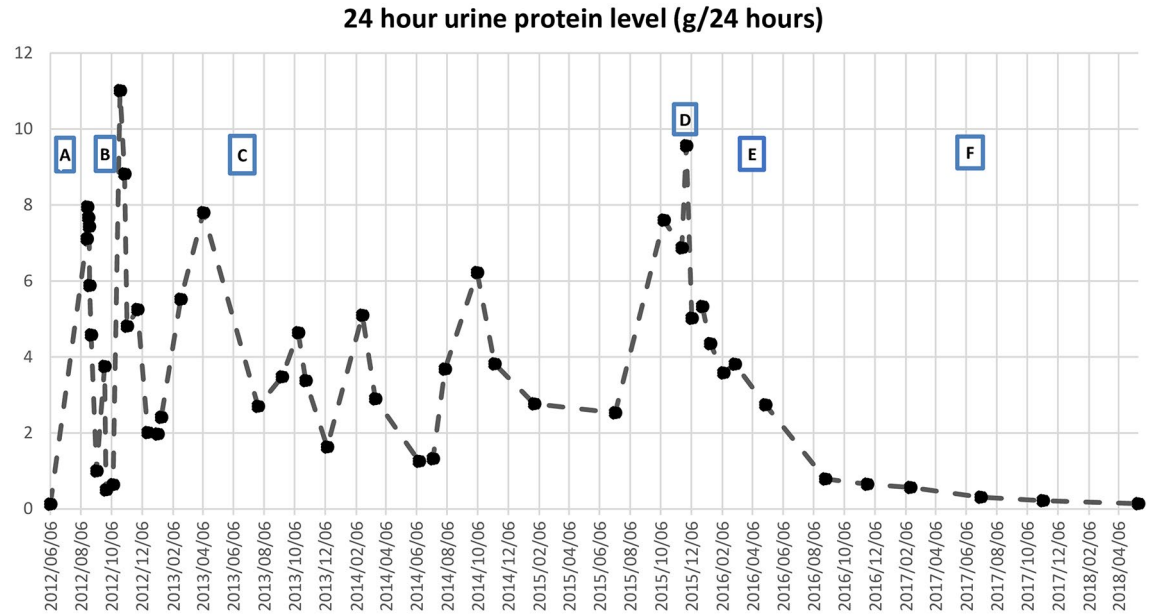

Fig. 1 **A**: Extended right hemicolectomy, **B**: Left hemicolectomy, **C**: Radiofrequency ablation left kidney, **D**: Neoadjuvant chemotherapy for gastric cancer, **E**: Total gastrectomy, **F**: Wedge resection left lower lobe lung

colon tumor the level of proteinuria gradually decreased (Fig. 1).

In the beginning of 2013 there was a recurrence of the nephrotic syndrome. A contrast enhanced CT scan showed a small (1 cm) hypervascular lesion in the left kidney, highly suspect for T1 renal cell carcinoma. A FDG-PET scan showed no increased FDG-avidity in this lesion or abnormal FDG-avidity elsewhere. The renal lesion was subsequently treated with radiofrequency ablation in June 2013 (Fig. 1 point C). In the following months 24 h urine protein levels fluctuated, but overall the nephrotic syndrome slowly improved with conservative treatment.

In October 2015 the nephrotic syndrome relapsed again and a second renal biopsy was taken. This kidney biopsy contained 43 glomeruli of which 5 were globally sclerosed indicative of disease-related progression (a maximum of 3 sclerosed glomeruli could be expected at the age of 45) [6]. Contrary to the initial kidney biopsy, the hilus of some glomeruli were hyalinized and some podocytes had a foamy appearance, but no definite segmental sclerosis could be identified and therefore again a diagnosis of minimal change disease was made, albeit with minor progression to global glomerulosclerosis. A PET-CT scan and gastroscopy were performed because recurrent cancer was suspected, and this time an intestinal type adenocarcinoma with signet ring cell differentiation in the cardia of the stomach (ypT3N0M0) was diagnosed. He was treated with neoadjuvant chemotherapy (Fig. 1 point D) followed by total gastrectomy (Fig. 1 point E) and adjuvant chemoradiotherapy. After this treatment the proteinuria progressively declined until resolution of the nephrotic syndrome (Fig. 1).

One year later a CT scan showed a growing nodule in the left lower lobe of the lung and in the laboratory results there was an increase in CEA level. A wedge resection was performed, because of the suspicion of a metastasis (Fig. 1 point F). This turned out to be a pT1bN0M0 primary lung adenocarcinoma. During this episode he did not experience a relapse of the nephrotic syndrome. In the beginning of 2023, two other pT1 adenosquamous lung carcinomas were surgically removed. Both were primary lung carcinomas with a different molecular profile (see Table 1 for more details regarding the tumor characteristics). Despite these new malignancies he did not have a recurrence of the nephrotic syndrome.

We performed immunohistochemical staining of the different resected tumor specimens using an antibody specific for vascular endothelial growth factor (VEGF) as described before using the mouse anti-human VEGF (C-1) from Santa Cruz [7]. This staining revealed strong VEGF expression in the gastrointestinal tumors, but not in the three independent lung cancer and the cutaneous squamous cell cancer specimens (Fig. 2).

Discussion

This is, to our knowledge, the first case report of a Lynch syndrome patient with recurrent paraneoplastic nephrotic syndrome caused by minimal change disease. In our patient the decreased creatinine clearance (eGFR MDRD 20 ml/min/1,73m2) and the increased level of proteinuria repeatedly functioned as an early warning sign for tumor activity.

Paraneoplastic nephrotic syndrome can present before, concomitant with or after cancer diagnosis. Cozzo et al. found in their systematic review that in 31.4% of the cases tumor diagnosis followed minimal change disease diagnosis by 12.4 ± 22.6 months [3]. It may take months before the nephrotic syndrome completely resolves after curative treatment, often without any additional treatment apart from the cancer treatment [2, 3, 8, 9].

The first association of malignant tumors and nephrotic syndrome has been described in 1966 by Lee et al. During a ten year period, they found an underlying malignancy in 11% of nephrotic syndrome patients. The authors suggest that the nephrotic syndrome could be a paraneoplastic phenomenon caused by an immune response of the host to the neoplasm [10].

The most common glomerulopathy associated with solid tumors is membranous nephropathy, whereas minimal change disease is more frequently associated with lymphoma [2]. In a recent systematic review 86 cases of paraneoplastic minimal change disease in a patient with solid tumors were described. Tumors most frequently associated with paraneoplastic minimal change disease were malignancies of the thymus (34.9%), kidney (14%), lung (12.8%) and gastro-intestinal tract (12.8%) [3]. In our case the gastrointestinal tumors and the renal cell tumor indeed caused a paraneoplastic minimal change disease, but the three lung carcinomas did not. This is surprising as lung cancer is also one of the tumors associated with paraneoplastic minimal change disease [2, 3].

In children, minimal change disease is the most common cause of nephrotic syndrome. Cheong et al. describe that plasma vascular endothelial growth factor (VEGF) concentration was significantly higher in a group of children in the active nephrotic phase compared to those in remission. They suggest that circulating VEGF is associated with proteinuria [11]. These findings in childhood minimal change disease were confirmed by others, who suggested that VEGF is likely to play a role in glomerular permeability and the induction of proteinuria [12, 13].

The exact pathogenesis of paraneoplastic minimal change disease is unknown. It has been proposed that systemic disorder of T lymphocyte function plays a role. Circulating cytokines, tumor antigens and growth factors can injure the glomerular basement membrane and podocytes

Table 1 Overview of tumor characteristics

Date	Specimen	Tumor characteristics	Immunohistochemistry	Next generation sequencing (with Ampliseq Cancer Hotspot (v6 panel))
2009	Excisional biopsy abdominal skin	Squamous cell carcinoma	Normal expression of MLH1, PMS2, MSH2, MSH6	-
June 2012	Endoscopic biopsies ascending colon	Intestinal type adenocarcinoma	Normal expression MSH2 and MSH6 Weak expression PMS2 and MLH1	-
July 2012	Resection specimen right hemicolectomy	Adenomatous polyp with high grade dysplasia	Normal expression MSH2 and MSH6 Weak expression PMS2 and MLH1	-
September 2012	Resection specimen left hemicolectomy	Poorly differentiated adenocarcinoma	Normal expression MLH1, MSH2, MSH6 Weak expression PMS2	-
June 2013	Biopsy of lesion in left kidney during RFA	Extrarenal tissue; sampling error	-	-
December 2015	Endoscopic biopsies cardia of the stomach	Poorly differentiated intestinal type adenocarcinoma with signet ring cell differentiation	Normal expression MLH1, MSH2, MSH6 Weak expression PMS2 Her2neu negative CDX2 positive	-
April 2016	Resection specimen total gastrectomy	Poorly differentiated intestinal type adenocarcinoma (Mandard tumor regression grade 4)	Her2neu negative	-
June 2017	Resection specimen wedge resection left lower lobe of the lung	Adenocarcinoma	Normal expression MSH2, MSH6 Heterogenous loss of expression MLH1 and PMS2 TTF-1 positive, CDX2 negative PDL-1 TPS < 1%	TP53 (c.871 A > T, p.(Lys291*))
September 2022	Excisional biopsy neck skin	Squamous cell carcinoma	-	-
January 2023	Resection specimen wedge resection left lower lobe of the lung	Adenosquamous carcinoma	Normal expression MLH1, PMS2, MSH2, MSH6 TTF-1 positive, p40 positive, p63 positive, CDX2 negative PDL-1 TPS > 80%	TP53 (c.524G > A, p.(Arg175His)), PTEN (c.955_958delACTT, p.(Thr319*)), RB1 (c.763 C > T,p.(Arg255*))
February 2023	Resection specimen wedge resection right lower lobe of the lung	Adenosquamous carcinoma	TTF-1 positive, p40 and p63 mostly negative PDL-1 TPS > 90%	KRAS (c.34G > T, p.(Gly12Cys)), TP53 (c.472 C > G,p.(Arg158Gly)) DNA analysis showed no mutation in STK11 of EGFR

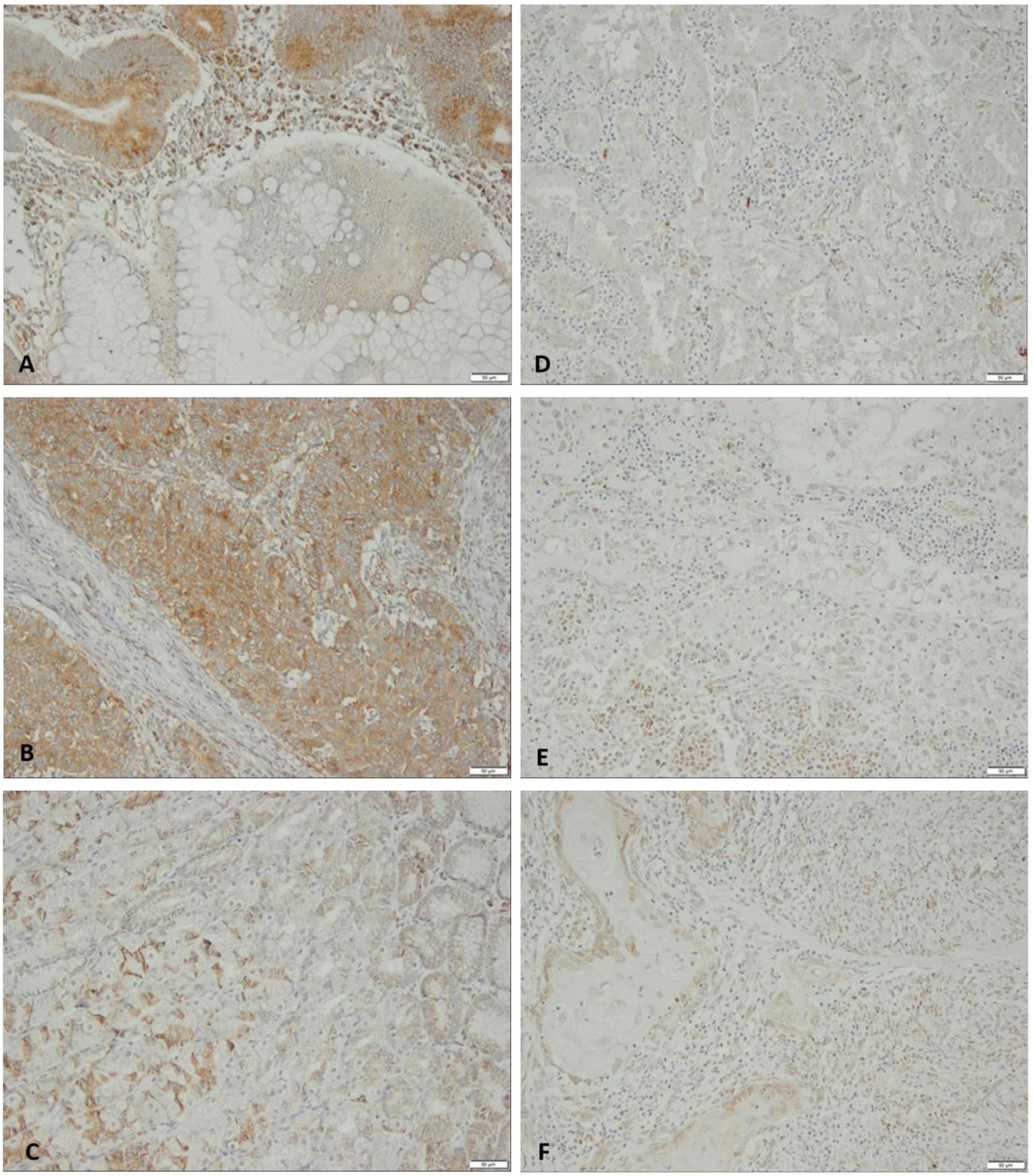

Fig. 2 Immunohistochemical staining for vascular endothelial growth factor (VEGF): **A** t/m C gastrointestinal cancers showing high VEGF expression in the epithelial cancer cells; D t/m F non-gastrointestinal cancer specimens showing low VEGF expression. **A**: resection specimen right hemicolectomy showing high grade dysplasia, **B**: resection specimen left hemicolectomy with colon cancer, **C**: resection specimen gastric carcinoma, **D**: resection specimen lung carcinoma February 2023, E: resection specimen lung carcinoma January 2023, **F**: biopsy cutaneous squamous cell carcinoma. Scale bar 50 µm

resulting in altered glomerular permeability to protein [2–4]. VEGF is such a circulating endothelial growth factor that has been linked to the development of glomerulopathies once it is overexpressed or reduced [14]. It is expressed in

podocytes and renal tubular epithelial cells and plays a role in endothelial cell differentiation, angiogenesis and vascular permeability. Tight control of VEGF signaling in the kidney seems to be essential for maintaining optimal glomerular membrane permeability.

Taniguchi et al. reported a patient with minimal change disease who had advanced rectal cancer and elevated VEGF levels. After surgery of the underlying tumor the nephropathy quickly remitted and VEGF levels normalized. Immunohistochemistry showed a high expression of VEGF in the rectal cancer cells which might have been the underlying cause for the paraneoplastic nephropathy [9].

To test this hypothesis in our case we measured the expression of VEGF in the available tumor specimens of our patient. In our patient, we demonstrated a strong expression of the VEGF protein in the specimens of the gastro-intestinal tumor, but not in any of the lung cancer specimens or in the cutaneous squamous cell cancer (Fig. 2). As this VEGF expression pattern coincides with the occurrence of the nephrotic syndrome, a causal relationship is suggested, which is in line with previous observations [9, 11–13].

In conclusion, this case report not only emphasizes the importance of considering an underlying malignancy in patients presenting with a nephrotic syndrome, especially in patients who are at an increased risk of developing malignancies, like Lynch syndrome patients, but also provides further evidence for a causative role for VEGF in the pathogenesis of paraneoplastic minimal change disease.

Author contributions M.J. and A.L. wrote the main manuscript text. M.S., M.N., A.C., A.R, and A.L. were all treating physicians of this patient and made the multidisciplinary approach of this case possible. E.J. and L.H. did the immunohistochemical staining and prepared Fig. 2. L.H. and A.C. analysed the results of the immunohistochemical staining. A.C. provided all the pathology samples. All authors reviewed the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Informed consent The patient approved of the publication of this case report by providing oral consent. This consent has been documented in his patient file.

Competing interests The authors declare no competing interests.

References

1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases Kidney Int 100:1–276. https://doi.org/10.1016/j.kint.2021.05.021
2. Bacchetta J, Juillard L, Cochat P, Droz JP (2009) Paraneoplastic glomerular diseases and malignancies. Crit Rev Oncol Hematol 70:39–58. https://doi.org/10.1016/j.critrevonc.2008.08.003
3. Cozzo D, Orlando F, Bruno M et al (2024) Minimal change glomerular disease associated with solid neoplasms: a systematic review. J Nephrol. https://doi.org/10.1007/s40620-024-02084-6
4. Yong TY, Khow KSF, Li JYZ (2012) Minimal change disease as a paraneoplastic manifestation of solid malignant tumors. Nephrol Res Reviews 4:27–32. https://doi.org/10.4081/nr.2012.e6
5. Lynch HT, de la Chapelle A (2003) Hereditary colorectal cancer. N Engl J Med 348:919–932. https://doi.org/10.1056/NEJMra012242
6. Hommos MS, Zeng C, Liu Z, Troost JP, Rosenberg AZ, Palmer M, Kremers WK, Cornell LD, Fervenza FC, Barisoni L, Rule AD (2018) Global glomerulosclerosis with nephrotic syndrome; the clinical importance of age adjustment. Kidney Int 93(5):1175–1182. https://doi.org/10.1016/j.kint.2017.09.028
7. Hawinkels LJ, Zuidwijk K, Verspaget HW, de Jonge-Muller ES, van Duijn W, Ferreira V, Fontijn RD, David G, Hommes DW, Lamers CB, Sier CF (2008) VEGF release by MMP-9 mediated heparan sulphate cleavage induces colorectal cancer angiogenesis. Eur J Cancer 44:1904–1913. https://doi.org/10.1016/j.ejca.2008.06.031
8. Glassock RJ (2003) Secondary minimal change disease. Nephrol Dial. https://doi.org/10.1093/ndt/gfg1060. Transplant18:52–8
9. Taniguchi K, Fujioka H, Torashima Y, Yamaguchi J, Izawa K, Kanematsu T (2004) Rectal cancer with paraneoplastic nephropathy: association of vascular endothelial growth factor. Dig Surg 21:455–457. https://doi.org/10.1159/000083474
10. Lee JC, Yamauchi H, Hopper J Jr (1966) The association of cancer and the nephrotic syndrome. Ann Intern Med 64:41–51. https://doi.org/10.7326/0003-4819-64-1-41
11. Cheong HI, Lee JH, Hahn H, Park HW, Ha IS, Choi Y (2001) Circulating VEGF and TGF-beta1 in children with idiopathic nephrotic syndrome. J Nephrol 14:263–269
12. Farid F, Baky AA, Fawzy M, Mostafa R (2019) Study of circulating vascular endothelial growth factor in Nephrotic Children. EC Paediatrics 8(1):30–37
13. Ruslie RH, Darmadi D, Siregar GA (2021) Vascular endothelial growth factor (VEGF) and Neopterin Levels in children with steroid-sensitive and steroid-resistant nephrotic syndrome. Med Arch 75(2):133–137. https://doi.org/10.5455/medarh.2021.75.133-137
14. Estrada C, Maldonado A, Mallipattu SK (2019) Therapeutic inhibition of VEGF signaling and Associated Nephrotoxicities. J Am Soc Nephrol 30(2):187–200. https://doi.org/10.1681/asn.2018080853