To date, a systematic nephrological or gynaecological treatment for this type of patient has yet to reported in the medical literature.[9]

Various measures are mentioned in publications, such as: increase the erythropoietin dosage, increase dialysis time, use low ultrafiltration rates to improve blood volume control, avoid hypotension events, reduce liquid intake restrictions and maintain low predialysis urea levels.[9,10,12,13]

Pregnancy during dialysis continues to be rare and it occurs in various units. This makes it a difficult research point,[14] but nevertheless these pregnancies should be included in a register, in the same way that other Societies and the EDTA have done.

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B) BRIEF CASE REPORTS

Nephropathy following administration of angiogenesis inhibitors

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To the Editor,

Angiogenesis has an important role in metastasis development. In recent years, the vascular endothelial growth factor (VEGF) has become one of the main objectives in treating tumour-induced angiogenesis.

Various studies have shown that the anti-VEGF monoclonal antibody, bevacizumab, can reduce angiogenesis and inhibit solid tumour growth.[1]

Various secondary effects have been associated with bevacizumab use. Two of the most common effects are moderate proteinuria (up to 64% of cases) and hypertension. Nephrotic-range proteinuria only occurs in 1%-2% of bevacizumab-treated patients.[2]

We present the case of a 42-year-old man, diagnosed with grade II fibrosarcoma in the thigh and left-scapular region in November 1999. Tumour resection was indicated.

Three years later, he developed progressive pulmonary metastatic disease, which was treated with surgery and chemotherapy (MAID protocol: mesna, adriamycin, ifosfamide and dacarbazine).

In May 2004, he developed progressive pulmonary metastatic disease again and was treated with taxotere and gemcitabine, completing 6 cycles. He

then completed 21 cycles of therapy with gemcitabine only.

In August 2008, he started gemcitabine and bevacizumab treatment, due to a disease relapse.

Following the second bevacizumab dosage, the patient was admitted due to headache, arterial hypertension (AHT) (BP: 190/100mm Hg) and general oedema. Upon admission, he had creatinine at 1.8mg/dl, nephrotic-range proteinuria and microhaematuria. Moderate normocytic/normochromic anaemia without schistocytes on the peripheral blood smear. Kidney ultrasound was normal. Immunological study only had low C3 levels. He had no previous history of AHT or kidney disease.

On the sixth day of his hospital stay, a renal biopsy was performed finding mesangiocapillary glomerulonephritis type II.

Gemcitabine and bevacizumab treatment was suspended and angiotensin II receptor antagonist (ARA-II) treatment started. Renal function improved, finally reaching creatinine levels of 1.1mg/dl; proteinuria decreased significantly and optimum blood pressure control was achieved.

Proteinuria in anti-VEGF-treated patients has been related to damage in the podocyte-endothelial-VEGF axis. VEGF production by podocytes is necessary for the glomerular endothelial to remain intact.[2] VEGF is expressed in the podocytes and its receptors are found in the endothelial cells of the normal glomerular capillaries.[3] When VEGF binds to its receptor, it promotes an increase in the microvasculature's permeability, cell migration and division, apoptosis inhibition and endothelial damage repair.[4]

In animal studies, a defect in the VEGF expression causes glomerular diseases characterised by nephrotic-range proteinuria, endotheliosis and hyaline deposits, which are similar to the kidney damage found in pre-eclampsia patients.[5]

We only found a few glomerulonephritis cases associated with anti-VEGF antibodies in the medical literature, and most were thrombotic microangiopathies. Bevacizumab-induced mesangiocapillary glomerulonephritis seems to be very rare. We believe that more cases will gradually appear due to the increased use of these antibodies in oncology in recent years.

Proteinuria which appears as a result of bevacizumab-induced glomerular damage seems to be reversible, at least partially, when this chemotherapy agent is suspended.

Our case, and other similar cases of patients with metastasis which develop bevacizumab-induced proteinuria had been treated with other, potentially nephrotoxic agents. Our patient also received high doses of gemcitabine over a long period of time. Little is still known about gemcitabine's mechanism of action on kidney damage, although we know that it is dose-dependent. In most cases, it is associated with haemolytic uremic syndrome,[6] although we have also found isolated cases associated with mesangiocapillary glomerulonephritis.[7]

Given that a kidney biopsy was not performed before bevacizumab treatment, we are not able to confirm that gemcitabine was not responsible for the patient's symptoms. However, given that the kidney damage was not evident until the start of anti-VEGF antibody treatment, we believe that the agent responsible for these symptoms was bevacizumab. It is possible that gemcitabine treatment produces initial renal damage, which may have been exacerbated by bevacizumab administration.

We recommend a strict control of the arterial pressure and kidney function in patients undergoing monoclonal antibody therapies.

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