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SCIENTIFIC LETTERS

Discordance between creatinine and cystatin C in patients with leukemia

Discrepancia entre creatinina y cistatina C en pacientes afectos de leucemia

Dear Editor:

The assessment of glomerular filtration is a necessary practice in oncological patients, given the nephrotoxicity of the drugs used for treatment and its usefulness in guiding prescribing. We present 3 cases in which there was a discrepancy between creatinine and cystatin C-based estimates in patients with a history of acute myeloid leukaemia (Table 1).

The first was a girl aged 11 years, with no personal or family history of renal or urinary tract disease, who, prior to initiation of treatment, exhibited abnormal levels of cystatin C as high as 2.74 mg/L (turbidimetric assay traceable to ERM-DA471/IFCC), with repeated measurements of creatinine within the normal range (0.55—0.65 mg/dL) (enzymatic assay traceable to IDMS). Blood pressure measurements were within the normal range and the patient had not lost a significant amount of weight. Blood chemistry tests ruled out thyroid disorders and the routine urinalysis revealed mild proteinuria that was likely to be due to hyperfiltration secondary to hyperhydration. Steroid therapy has not been initiated. A renal ultrasound scan showed mild nonspecific echogenicity of the renal parenchyma. Last of all, filtration was measured by means of Cr-ethylenediamine tetraacetic acid (EDTA) scintigraphy, yielding a value of 102 mL/min/1.73 m^2, which confirmed normal glomerular filtration, and the patient started treatment and has been free of nephrological complications to date.

The second was a boy aged 12 years who had undergone allogeneic haematopoietic stem cell transplantation (HSCT) one year prior and was in remission at the time he was referred to our clinic due to progressive worsening of renal function as inferred by the cystatin C level (1.44 mg/L) while the creatinine level remained stable (0.43 mg/dL). This was initially attributed to different drugs: baricitinib, used for treatment of cutaneous graft versus host disease, and acyclovir used for prophylaxis. His weight and blood pressure were within the normal range. The results of the blood and urine tests were normal, thyroid disease was ruled out and the patient was not receiving steroids. The glomerular filtration rate was measured with Tc-99 diethylenetriaminepentaacetic acid (DTPA) scintigraphy, which yielded a value of 135 mL/min/1.73 m^2, within the normal range.

The third patient was a young woman aged 20 years with leukaemia secondary to osteosarcoma of the right femur, both in remission, who had undergone HSCT 2 years before. In recent follow-up visits, there had been a progressive increase in the levels of cystatin C to up to 1.74 mg/L, while creatinine levels remained stable at 0.5 mg/dL. The patient had normal anthropometric measurements and did not have hypertension. She was in treatment with levothyroxine for hypothyroidism, with adequate control. There were no urinary abnormalities and the renal ultrasound scan showed mild hyperechogenicity. The patient was not on steroid therapy. Suspending the nephrotoxic drugs she was receiving for prophylaxis, acyclovir and posaconazole did not resolve the discrepancy, which prompted measurement of the GFR with Tc-99 DTPA scintigraphy, the result of which was 85 mL/min/1.73 m^2, a value in between those estimated based on the cystatin C and creatinine levels and indicative of mild chronic renal disease.

Cystatin C is a low molecular weight protein synthesised by all nucleated cells. It is considered the ideal endogenous marker of glomerular filtration, as it is freely filtered in the renal glomeruli and almost completely reabsorbed and catabolized in the proximal tubules, while its levels appear to be independent from sex, age, muscle mass or dietary habits.[1] However, cystatin C may be elevated not only in the context of renal impairment, but also of thyroid disorders or with the use of corticosteroids.[1,2] In the field of oncology, it has been found to play opposite roles in multiple types of cancer, as both a tumour suppressor and a tumour promoter.[3] Thus, cystatin C may have a protective effect by inhibiting the activity of lysosomal cysteine proteinases, which have been found to be associated with tumour progression and metastasis.[3] Its elevation unrelated to glomerular filtration has been described previously in adults with solid and blood tumours before initiation of treatment[1,2] and as a result of chemotherapy.[4] Different case series have found a subsequent descent in patients in remission.[1,2] Thus, cystatin C may be useful as a biomarker[3] and indicator of tumour burden.[2]

Last of all, there are specific circumstances in which accurate measurement of the glomerular filtration rate is required, which can be achieved by measurement of an exogenous marker, such as radioactive tracers like Cr-EDTA or Tc-99 DTPA, which yield values that are in agreement with each other, or iodinated contrast agents, such as the plasma clearance of iohexol, which is strongly correlated to the urinary inulin clearance.[5]

We present the cases of 3 patients with leukaemia in whom glomerular filtration rate estimates were corroborated using isotopic markers. The discrepancy with the

Table 1 Characteristics of the patients.

Patient	Diagnosis	Weight in kg (percentile, z-score)	Height in cm (percentile, z-score)	BMI in kg/m^2 (percentile, z-score)	BP in mmHg	Baseline serum creatinine (mg/dL)	eGFR based on creatinine (FAS_{crea} 2016)	Cystatin C (mg/L)	eGFR based on cystatin C (FAS_{cycC} 2017)	eGFR based on creatinine and cystatin C combined (FAS_{combi} 2017)	eGFR based on imaging techniques
1	Acute myelomonocytic leukaemia	40.75 (P42; −0.21)	147 (P44; −0.16)	18.86 (P45; −0.15)	103/53	0.65	90	2.74	32	47	102
2	Acute myeloblastic leukaemia	39 (P21; −0.81)	143 (P8; −1.44)	19.07 (P39; −0.28)	100/66	0.43	131	1.44	61	86	135
3	Osteosarcoma/ Secondary acute myeloid leukaemia not otherwise specified	56 (P43; −0.19)	157 (P12; −1.19)	22.72 (P68; 0.48)	99/64	0.53	142	1.74	51	75	85

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate.
The eGFR is expressed as mL/min/1.73 m^2 and was calculating based on the creatinine level, cystatin C level or both combined through the Full-Age Spectrum (FAS) equations[6] published in 2016 and 2017, respectively, with the corresponding adjustment for height of the FAS_{crea} in patients 1 and 2 ($FAS_{crea\text{-}height}$), and the FAS_{combi}.

estimates obtained based on the level of creatinine highlight the need to interpret cystatin C levels with caution in the context of malignancy, both at diagnosis and during the follow-up, and the need to introduce new markers in everyday clinical practice that provide a more accurate assessment of glomerular filtration.

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Cutaneous and hepatic infantile haemangiomas as a clinical manifestation of Beckwith Wiedemann syndrome

Hemangiomas infantiles cutáneos y hepáticos como manifestación clínica de síndrome de Beckwith-Wiedemann

Dear Editor:

Infantile haemangiomas (IHs) are the most frequent type of benign tumours in children; however, they may be problematic, leading to complications such as ulceration, functional impairment, hypothyroidism or disfigurement, in which case propranolol is the first-line treatment. In addition, IHs, depending on the location, may be associated to other diseases such as PHACE syndrome, LUMBAR syndrome or, if there are 5 or more cutaneous lesions, liver haemangioma. Screening ultrasonography is recommended to rule the latter out.[1]

We present the case of an infant aged 3 months with asymptomatic cutaneous lesions with a vascular appearance present from birth. The salient personal history included conception with assisted reproductive technology (ART), delivery by caesarean section due to suspected subclinical chorioamnionitis (week 28^{+2}), large weight and length for gestational age (at the 92th and 98th percentiles), umbilical hernia, mild macroglossia and hyaline membrane disease treated with one dose of surfactant. The family history was unremarkable. The physical examination revealed 7 purplish-red papules with a vascular appearance, 2–6 mm in diameter, located in the right palm, penis, back, clavicle and right shoulder, compatible with multiple IHs (Fig. 1).

Due to the presence of more than 5 haemangiomas, an ultrasound examination of the abdomen was performed, revealing between 10 and 15 space-occupying lesions, hypoechogenic, oval, some with a Doppler signal within, compatible with hepatic haemangioma (Fig. 2A and B). The complete blood count, thyroid and liver function panels and the alpha-foetoprotein test did not detect any relevant abnormalities. Early treatment was initiated with oral propranolol at a dose of 1 mg/kg every 12 h for a duration of 1 year, with resolution of the hepatic haemangiomas within 4 months (Fig. 2C and D) and progressive regression of the cutaneous haemangiomas. Given the presence of macroglossia, umbilical hernia and macrosomia, the patient exhibited 1 cardinal feature and 2 suggestive features (4 points in total) for the diagnosis of Beckwith-Wiedemann syndrome (BWS). When a patient has a score of 4 points or greater, it is possible to make a clinical diagnosis of BWS without awaiting the results of genetic testing, although testing is still recommended.[2] Testing of the 11p15.5 locus by means of methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) evinced loss of methylation of the imprinting control region 2 (ICR2), compatible with BWS.

Beckwith-Wiedemann syndrome is the most frequent overgrowth syndrome, with a prevalence of 1 case per 10 340 naturally conceived births and 1 case per 1126 births from ART.[3] It is characterised by macroglossia, macrosomia, abdominal wall defects, neonatal hypoglycaemia and