



Figure 1 Chest CT images (axial and coronal views) showing a 4 × 2 mm nodule in the upper left lobe.

high-resolution thyroid ultrasound examination.⁴ Detectable calcitonin levels indicate the presence of distant metastases, and require performance of CT of the neck, mediastinum, lung and liver, and in case a suspicious nodule is detected, an ultrasound-guided fine needle aspiration biopsy.⁵ In our patient, a lung nodule was detected and resected under CT guidance, which examination identified as a tuberculous necrotising epithelioid cell granuloma.

When patients develop isolated metastases, these should be resected, as radiotherapy and chemotherapy are used as palliative measures. Tyrosine-kinase inhibitors⁶ have been approved by the FDA for the treatment of metastatic MTC in adults, but have not been authorised for use in the paediatric population.

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Hepatic involvement in a female carrier heterozygous for a mutation in the *PHKA2* gene[☆]



Afectación hepática de paciente portadora en heterocigosis de una mutación en el gen *PHKA2*

Dear Editor:

Glycogen storage diseases (GSDs) are a group of hereditary diseases characterised by abnormalities in glycogen

metabolism. Glycogen storage disease type IX, which is caused by a defect in glycogen phosphorylase kinase (PHK), accounts for 25% of GSD cases, and the most frequent subtype is *PHKA2* (GSDIXa; OMIM: 306000) with a recessive X-linked inheritance pattern.¹ The phenotype of these patients ranges from mild forms presenting with hepatomegaly and elevation of liver enzyme levels to more severe forms that manifest with hypoglycaemia, short stature and mild gross motor delays.² Other possible manifestations include high blood cholesterol, triglyceride levels and ketosis following breakfast.³ Symptoms usually improve with age, although some patients develop liver tissue fibrosis that may progress to cirrhosis.¹

There are very few descriptions of females affected by GSDIXa in the literature, but those with heterozygous mutations may have disease manifestations in a wide spectrum.⁴ In these cases, X chromosome inactivation could play an important role in disease

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expression, although many other biological events are at play.⁵

We present the clinical case of a girl whose relevant family history consisted of a brother with GSD type IXa and consanguinity (the father was the son of a first cousin of the mother). Onset in the brother occurred at age 14 months with abdominal distension, hepatomegaly, hypertransaminasemia and hypertriglyceridaemia and episodes of hypoglycaemia. A liver biopsy was performed, the results of which were compatible with GSD, followed by genetic testing that confirmed the diagnosis of GSDIXa with a hemizygous c.1404dupT mutation in gene *PHKA2*. His sister was seen in the office for the first time at age 4 months. Relevant findings in this visit included hepatomegaly, with the liver extending 3 cm below the costal margin, a reported absence of manifestations of hypoglycaemia, and adequate weight and height. Blood testing revealed elevated transaminase levels (GOT, 131 U/L; GPT 74 U/L) and levels of CPK, glucose, cholesterol and triglycerides within normal ranges. The evaluation was completed with an abdominal ultrasound scan, which showed diffuse changes in echogenicity in the liver. The patient was fitted with a transcutaneous 3-day continuous glucose-sensing system that did not detect any episodes of hypoglycaemia. During the follow-up period, hepatomegaly progressed to up to 5 cm along with an increase in transaminase levels, which peaked at 212 U/L for got and 144 U/L for GPT, while the patient remained asymptomatic. Genetic testing was ordered on account of the positive history of GSDIXa in her brother, confirming the presence of a heterozygous c.1404dupT mutation in the *PHKA2* gene. The patient was given dietary recommendations, including a maximum duration of 8 h for fasting periods and the intake of low-burning carbohydrates before bedtime. The patient remained asymptomatic during follow-up, with adequate physical and psychomotor growth and persistence of mild hypertransaminasaemia and hepatomegaly at nearly 3 years of age. Her brother had equally favourable outcomes, with catch-up growth in height from a z-score of -1.39 to a z-score of -0.11 in the last checkup at age 5 years. However, the brother did have recurrent episodes of hypoglycaemia, some of which even required overnight continuous enteral feeding due to his difficulty in achieving an adequate oral intake.

Diseases with a recessive X-linked pattern of inheritance usually produce symptoms only in males. In females, the molecular mechanism known as X chromosome inactivation, which consists of the random transcriptional silencing of one of the X chromosomes, inactivates either the healthy or the abnormal chromosome, and if the number of cells in which the normal gene is inactivated is higher, the disease may manifest.⁴ There is a published case of a female patient with a heterozygous c.3614C>T mutation

in the *PHKA2* gene that presented with hepatomegaly and abnormal liver function during childhood, both of which normalised gradually. Molecular testing detected skewed X-chromosome inactivation in the patient, in contrast with a normal inactivation pattern in her sister, who had the same heterozygous mutation but remained asymptomatic.⁴

Thus, it is important to perform carriage testing in females, as some of them may develop manifestations of GSDIXa of varying severity, which may be associated to the degree of skewed X chromosome inactivation,¹ an association that has not been found in some studies of other X-linked hereditary disorders.⁵ It also makes genetic counselling possible.¹ Recently developed next generation sequencing (NGS) methods are now the gold standard for confirming the diagnosis of GSDs, replacing the invasive methods used in the past, such as liver biopsy.⁶

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