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Medullary thyroid carcinoma in a 6-year-old boy with previous Langerhans cell histiocytosis presenting high level of pro-calcitonin

Rak rdzeniasty tarczycy u 6-letniego chłopca z przebytą histiocytozą z komórek Langerhansa, przebiegający z wysokim stężeniem prokalcytoniny

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Abstract

Objectives: To describe medullary thyroid cancer (MTC) onset in a boy affected previously by Langerhans cell histiocytosis (LCH) and review the literature for other reports of this association.

Case presentation: A 6-year-old boy was treated for LCH diagnosis when he was 4 years old. After treatment, a rise in procalcitonin levels was observed (2.36–2.78 ng/ml) initially interpreted as inflammatory response. Further procalcitonin increase (4.61 ng/ml) with cervical lymphadenopathy and no infective focus was suspicious of thyroid involvement, confirmed by ultrasound, serum calcitonin, and cytological diagnosis. Total thyroidectomy with bilateral lymph node exeresis was performed. RET gene analysis revealed p.Met918Thr mutation. No association between the previous LCH and MTC had been identified to date.

Conclusions: MTC is a rare condition in childhood presenting with an aggressive behaviour. It becomes crucial to increase the awareness of its features and anticipate diagnosis. Therefore, persistent high levels of pro-calcitonin without infective/inflammatory focus should lead to suspicion of thyroid involvement.

Key words: procalcitonin, medullary thyroid cancer, calcitonin, paediatric age, Langerhans cell histiocytosis.

Introduction

Medullary thyroid cancer (MTC) is a rare paediatric tumour, with an incidence of 0.03 cases per 100,000 population per year [1]. In 95% of cases MTC is inherited, while the sporadic form is almost anecdotal in paediatric age. Inherited forms include familial MTC (FMTC) or multiple endocrine neoplasia type 2 due to mutations in the *RET* gene. More than 100 known mutations have been described, classified as highest (MEN2B), or high and moderate (MEN2A) risk for cancer development, of which nearly 50% are *de novo* [2, 3].

The most specific biochemical marker for MTC is calcitonin, a parafollicular thyroid C-cell secreted protein, but its detection has several limitations due to analytical, physiological, pathological, and pharmacological variables [4]. Basal serum determination is recommended for diagnosis and follow-up in MTC.

Once MCT is diagnosed, pheochromocytoma and hyperparathyroidism should be ruled out and *RET* gene analysis should be performed. Radiological evaluations include neck ultrasound, chest CT, abdominal MRI, and total body bone scintigraphy if mediastinal, abdominal, or bone metastases are suspected [5].

In inherited forms due to *RET* gene mutations, prophylactic thyroidectomy is recommended based on the underlying mutation [6]. Despite the prophylactic approach, microcarcinoma is often present, even if current recommendations are appropriately followed [7, 8]. Routine central lymph node resection is not recommended unless lymph node involvement is suspected by ultrasound or if serum calcitonin is elevated (> 40 pg/ml). A clinical diagnosis of MTC occurs more frequently in sporadic forms and in *de novo* mutations of the *RET* gene; in these cases, the surgical approach is more invasive because lymph node involvement is more frequent and is associated with a reduced survival rate [9]. In such cases, resection of the central and ipsilateral lateral lymph nodes should be performed, as well as contralateral lymphadenectomy, if calcitonin is above 200 pg/ml. Postoperative follow-up includes periodic measurement of calcitonin and CEA and ultrasound evaluation. The prognosis of MTC in childhood is significantly better when compared to adults due to smaller tumours and lower rates of lymph node metastases, even in the case of multifocal disease [10].

Medullary thyroid cancer is not sensitive to classical radiotherapy or chemotherapy; in recent years, tyrosine kinase in-

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hibitors (TKI) such as vandetanib and cabozantinib have been proposed for unresectable MTC or progressive metastatic disease [11].

In the present case report we describe a paediatric patient with an association, not yet reported in the literature, of MTC and a previous Langerhans cell histiocytosis, a clonal neoplasm of myeloid dendritic cells involving mostly bone, skin, pituitary gland, lymph nodes, liver, spleen, and lungs.

Bioethical standards

Parents written inform consent was obtained for the case description and Ethics Committee of the Health and Science City University Hospital of Turin approval was also obtained (nr. 98/2023).

Case description

A 6-year-old boy was referred to the paediatric endocrinologist for thyroid nodules detected during an ultrasound evaluation performed for bilateral cervical lymphadenopathy and persistent high level of procalcitonin. One nodule of size 1.5 × 0.9 cm was detected in the left lobe, with hypoechoic ultrasound pattern, and another nodule of size 0.9 × 0.5 cm in the right lobe, with the same ultrasound features. Bilateral lymphadenopathy (2.2 × 0.9 cm in the right side, 2.6 × 1 cm in the left) in the angolo-mandibular region was also detected.

The biochemical assessment showed normal thyroid hormone profile, negative titration of anti-peroxidase and anti-thyroglobulin antibodies, and elevated basal serum calcitonin 568 ng/l.

In the past medical history, a Langerhans cell histiocytosis in the parieto-occipital and mastoid part of the temporal bone was diagnosed bilaterally at the age of 4 years. The *BRAF V600E* gene mutation was identified on the bioptic tissue from an external auditory canal polyp. No other tumour-predisposing mutations were observed.

A 2-year chemotherapy was started, according to LCH-IV protocol, with prednisone, vinblastine, and mercaptopurine. For the presence of an anatomical communication between the dura mater and the middle ear, due to alteration of the mastoid bone, prophylactic antibiotic treatment was also started during chemotherapy.

The oncological follow-up shows a progressive rise in procalcitonin levels (2.36–2.78 ng/ml, normal values < 2). Because all negative culture investigations were negative, this increase was initially interpreted as an inflammatory response. After completion of the chemotherapy treatment, the boy presented abdominal distension and a small collection of fluids was detected in the right hepato-renal region.

A further increase of procalcitonin (4.61 ng/ml), not associated with inflammatory/infectious signs, and the presence of cervical lymphadenopathy therefore gave rise to the suspicion of thyroid involvement, confirmed by the initial ultrasound evaluation.

A fine needle biopsy was therefore performed with subsequent cytological diagnosis of medullary thyroid cancer (TIR5). Although the literature suggests that in a patient with medullary thyroid carcinoma under the age of 6 years the risk of lymph node metastases is low, considering the high levels of calcitonin (> 500) we decided to perform a total thyroidectomy with bilateral lymph node exeresis. TNM staging was pT1b (m), pN1b with involvement of the left latero-cervical lymph nodes, confirming the indication for excision of the lateral lymph nodes. Lung CT scan, abdominal and brain MRI, and total-body bone Tc^{99} scan were normal. Family history was negative for MTC, but genetic analysis of the *RET* gene revealed a heterozygous pathogenetic mutation, c.2753T>C (p.Met918Thr) in exon 16, consistent with MEN2B syndrome; both parents were tested but were negative for the identified *RET* mutation. The subsequent ophthalmological evaluation was normal, no gastrointestinal symptoms were present, but oral mucosal neurinomas were observed.

One year after the surgery, the serum calcitonin level is persistently low (< 15 ng/l), conventional treatment with calcium and vitamin D is necessary for the iatrogenic hypoparathyroidism, and abdominal ultrasound as well as urinary catecholamines are normal. No association between the previous LCH and MTC has been identified to date.

Discussion

Medullary thyroid cancer is present in 100% of patients affected by MEN2B with a more aggressive behaviour compared to other inherited forms [1, 2]. MEN2B syndrome is characterised by the association of medullary thyroid cancer, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromatosis, and Marphanoid habitus. The most frequent pathogenetic mutation of the *RET* gene in MEN2B syndrome is p.Met918Thr, classified by the American Thyroid Association as the highest-risk mutation [2]. A *de novo* mutation is detected in nearly 50% of patients; therefore, it is essential to increase awareness of the clinical and biochemical findings evocative of MEN2B syndrome for its early recognition.

The most sensitive biochemical marker of MTC is calcitonin, but its precursor, procalcitonin, and carcinoembryonic antigen (CEA) have also been used in diagnosis and follow-up [1].

Calcitonin measurement has several limitations due to rapid degradation *in vitro*, concentration-dependent half-life at room temperature, and several laboratory interferences. The upper limit of 15 ng/l has been proposed as the threshold for detection of all cases of MTC in adults. Serum calcitonin ranges of 20–50 ng/l and 50–100 ng/l have positive predictive values of 8.3 and 25%, respectively. A calcitonin level above 100 ng/l is correlated to at least one palpable thyroid nodule and, in this case, the positive predictive value is 100% [4]. Specific imaging for MTC metastases is necessary when calcitonin is above 500 ng/l at diagnosis, while 150 ng/l is the cut-off value for investigating metastases after prophylactic thyroidectomy [2]. The aforementioned cut-offs are based on studies in adults but are also used in the paediatric population as there are no specific cut-offs accepted for this age.

Procalcitonin has also recently been proposed as an alternative tumour marker in MTC follow-up. A strong correlation

has been observed between calcitonin and procalcitonin levels and, given the greater stability of this latter, it may represent a complementary marker of MTC [13].

In the reported patient, persistent increased levels of procalcitonin were detected during follow-up for LCH, lasting almost 12 months. This finding was initially attributed to an inflammatory response to the disease and its medical treatment. A further increase in procalcitonin without corresponding clinical features suggested the investigation of thyroid function and ultrasound evaluation. Bilateral nodules were detected with no clinically palpable thyroid mass. Cytological analysis was consistent with the diagnosis of MTC and histological assessment after total thyroidectomy confirmed the diagnosis. Considering the high serum calcitonin level (> 500 ng/l), lateral neck dissection was performed. Imaging for metastases search was negative. Genetic analysis of the *RET* gene revealed a mutation consistent with MEN2B syndrome, and specific follow-up was undertaken. One year after thyroidectomy, the patient is disease-free with persistently low calcitonin. Abdominal ultrasound was negative, and urinary catecholamines were normal.

To the best of our knowledge, this is the first case describing the association of MTC and LCH. Previously, many authors have reported for both children and adults the association of LCH and other tumours such as lymphoma, leukaemia, lung carcinoma, and papillary thyroid cancer (PTC), but none with MTC [14]. LCH increases the inflammatory response and may be responsive of autoimmune elicitation leading to Hashimoto's thyroiditis and subsequent increased risk of PTC. Furthermore, the *BRAF V600E* mutation is the most common molecular change in both PTC and LCH. Almost all reports describe the presence of both PTC and LCH in the thyroid gland. In the case described, the titration of anti-thyroid antibodies was negative, and no intra-thyroidal LCH was detected. The previous diagnosis of LCH, which could initially be compatible with an increased inflammatory state, a negative family history for MTC, and the absence of the typical signs of MEN2 in the patient can explain the initial diagnostic difficulty.

Medullary thyroid cancer in paediatric age has a well-defined phenotype-genotype correlation. MEN2B syndrome is mainly caused by *de novo RET* mutation, as in this patient. Given the greater aggressiveness of MTC in MEN2B syndrome, when a thyroid nodule is detected, calcitonin should always be evaluated, and typical clinical features should be carefully sought. However, the early identification of these features is challenging due to their gradual onset over time [15]. Clinical signs of this condition include musculo-skeletal features as Marphanoid habitus, pectus excavatum, scoliosis, long and narrow face, joint laxity, and proximal muscle weakness. Also, ganglioneuromas can occur in the lips, tongue, conjunctiva, and the urinary system as well as in the gastrointestinal tract, with constipation, feeding difficulties, and megacolon.

Because the presentation can also be atypical, as in the reported patient, in the case of persistent elevated procalcitonin with no strong clinical evidence, it becomes important to suspect it and carry out the measurement of calcitonin and possibly the subsequent ultrasound evaluation of thyroid.

Conclusions

Medullary thyroid cancer is a rare condition in childhood that can present with an aggressive behaviour, especially in the context of MEN2B syndrome, due to the early onset of metastases. As indicated in the guidelines for adults, in the case of high calcitonin levels and diagnosis of lymph node metastases, total thyroidectomy and bilateral lymph node exeresis could represent the surgical option even in paediatric age. Therefore, it becomes crucial to increase the awareness of its clinical, biochemical, and genetic features to anticipate diagnosis and to allow timely multidisciplinary management.

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