Clinical case

Nodular sclerosing Hodgkin’s disease mimicking Riedel’s invasive fibrous thyroiditis

Maladie de Hodgkin scléronodulaire mimant une thyroïdite fibreuse invasive de Riedel

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Abstract

Riedel’s thyroiditis appears in the form of a hard cervical mass with rapid onset, and it is associated with extensive fibrosis that compresses nearby structures, such as the trachea and supra-aortic vessels; its diagnosis is essentially histopathological. Although its histological characteristics have been well established, there are some diagnostic pitfalls. We report here the case of a 37-year-old woman, with clinical and histopathological data suggesting Riedel’s disease. Fibrosis regressed after treatment with corticosteroids, relieving the compressed airways. However, in contrast with the latest knowledge on this disease, the IgG4 serum levels were consistently normal, and positron emission tomography in search of extensive fibrosis revealed an abnormal metabolic activity of the bone marrow. The final diagnosis revised by the histopathologist was that of nodular sclerosing Hodgkin’s lymphoma. This case allows us to review the diagnostic approach when facing a thyroid mass with extremely rapid evolution.

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Résumé

La thyroïdite de Riedel se présente sous la forme d’une masse cervicale ferme d’apparition rapide associée à une fibrose extensive comprimant les structures avoisinantes comme la trachée et les vaisseaux supra aortiques ; son diagnostic est essentiellement anatomopathologique. Bien que la description histologique soit bien établie, des pièges diagnostics existent. Nous rapportons le cas d’une femme de 37 ans dont la présentation clinique et anatomopathologique plaidait pour une maladie de Riedel. La fibrose a régressé sous corticoïdes, libérant ainsi les voies respiratoires qui étaient comprimées. Cependant, en contraste avec les dernières connaissances au sujet de cette maladie, nous constatons que les taux sériques d’immunoglobulines IgG4 était constamment normaux et que la tomographie d’émission de positrons réalisée à la recherche d’une fibrose extensive révélait une activité métabolique anormale au niveau de la moelle osseuse. Le diagnostic final révisé par l’anatomopathologiste fut celui d’un lymphome Hodgkinien scléronodulaire. Ce cas nous permet de revoir une démarche diagnostique devant une masse thyroïdienne d’évolution torpide.

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1. Introduction

Riedel’s thyroiditis (RT) is a rare disease with a low incidence, estimated by some authors to be between 0.04 and 0.30% people [1]. The incidence reported was 0.06% people in the Mayo clinic’s series of thyroidectomies performed between 1920 and 1955. More recently, between 1976 and 2008, the
Mayo clinic [2] reported 21 cases with diagnosis of RT, according to its database. Despite its low incidence, the number of reported cases of RT is increasing, and authors are refining their means for diagnosis or proposing new therapeutic alternatives with glucocorticoids [3], such as tamoxifen [4], colchicine [5], azathioprine [6], mycophenolate mofetil [7] or, more recently, rituximab [8].

RT is characterized by lymphoplasmacytic infiltration of the thyroid, associated with extensive, systemic and local fibrosis [9]. It can be suspected in case of rapidly progressing, indurated and immobile goiter. The evolution can be marked by the appearance of symptoms such as tracheal compression with stridor, dysphonia due to laryngeal nerve damage, superior vena cava syndrome and, more rarely, clinical signs of hypocalcemia associated with infiltration of the parathyroid glands [10]. Thyroid dysfunction can also occur, most often as hypothyroidism (30% people) [1], with low serum levels of autoantibodies to thyroid peroxidase (TPO) in half of the patients.

Remotely, systemic fibrosis can occur, mainly in the form of retroperitoneal fibrosis, orbital pseudotumor, mediastinal fibrosis, pleuropericarditis or sclerosing cholangitis [6,11,12]. Based on this observation, some authors even propose to include RT in a more systemic pathology: hyperimmunoglobulinemia IgG4 syndrome or IgG4-related disease [13–17].

To date, only a histological examination can confirm RT, with the exception, perhaps, of an MRI, as hypodense signals on T1- and T2-weighted images could be pathognomonic [18,19]. There is no serum marker for the disease, apart from high IgG4 levels (usually over 1.35 g/L), although this point remains to be confirmed [13,17]. Fine-needle aspiration does not allow for definite diagnosis.

The differential diagnosis of a very hard thyroid mass also remains difficult to establish, as it includes sclerosing-type Hashimoto’s thyroiditis [20], sarcoma [21], sclerosing-type anaplastic carcinoma [22] and thyroid lymphoma [18,23–25].

2. Case report

We report the case of a 37-year-old woman who presented with a rapidly growing goiter, which had appeared 2 months earlier. Her family history revealed that her mother had undergone a thyroidectomy for benign nodules. The patient complained of asthenia and daytime hot flushes, and had recently presented with inspiratory dyspnea with stridor. She smoked one pack of cigarettes per day. No fever or general health deterioration was noted. Palpation revealed a hard, painless, immobile mass. Laboratory tests revealed TPO antibodies less than 10 UI/mL (< 35), free T4 at 11.9 pmol/L (7.8–18), thyroid-stimulating hormone (TSH) at 2.87 mUL (0.2–3.5), normal values for carcinoembryonic antigen (2.7 ng/mL, so < 4), and some calcitonin and calcemia.

Goiter ultrasonography revealed a lumpy heteronodular mass of 4.4 × 2.7 × 5 cm at the level of the isthmus and left lobe. This poorly vascularized mass comprised hypo- and hyperechogenic areas, as well as several small cystic areas. There was no adenopathy. The mass appeared as a cold spot by Technetium 99m scintigraphy. Fine-needle aspiration revealed an acellular material, and the absence of a definite diagnosis led to propose a thyroidectomy, which was finally impossible because of the highly adherent and fibrous aspects of the tissues.

Histological examination revealed a dense fibrous tissue along the striated muscle with atrophic fibers closely associated with nodular lymphoplasmacytic infiltrates. (Fig. 1). These characteristics strongly suggested a diagnosis of RT.

Fig. 1. Histological examination revealed a dense fibrous tissue along the striated muscle with atrophic fibers closely associated with nodular lymphoplasmacytic infiltrates.

Fig. 2. CT scan showed an infiltration process at the cervical and mediastinal levels, he mass was compressing the trachea and deflecting it to the right.
Fig. 3. The $^{18}$F-FDG-PET-CT confirmed the hypermetabolism of the bulky mediastinal mass.

Staging by cervicothoracic CT scan (Fig. 2) in search of systemic fibrosis revealed an infiltration process at the cervical and mediastinal levels, displacing and surrounding the supra-aortic arterial structures connecting to the pleura and extending along the left paraspinal line. The mass was compressing the trachea, deflecting it to the right.

Moderate abnormalities of pulmonary function (but typical of tracheal obstruction) were noted, with inspiratory and mostly expiratory limitation of the flow-volume loop. By tracheobronchial endoscopy, a 4-cm long extrinsic stenosis with a narrowing of more than 50% was detected, 5 cm below the vocal cords.

Positron emission tomography ($^{18}$F-FDG-PET-CT) confirmed the hypermetabolism of the bulky mediastinal mass (Fig. 3), with moderate tracer uptake. Tracer uptake was most prominent in the liver and particularly in the right hepatic lobe, which could be consistent with sclerosing cholangitis, although it was not confirmed by MRI. Moreover, the appearance of the bone marrow on $^{18}$F-FDG-PET-CT was abnormal.

Treatment with glucocorticoids (methylprednisolone) at 32 mg/day and colchicine at 1 mg/day was started to slow down the fibrotic process [3,5], and smoking cessation was initiated [4].

After eight weeks of treatment, the spirometry indicated a clear improvement of the flow-volume loop. The CT scan revealed that the lesion had decreased in size, both at the cervical ($65 \times 60$ mm vs. $85 \times 75$ mm) and mediastinal ($80 \times 60$ mm vs. $90 \times 73$ mm) levels.

However, laboratory tests showed serum IgG4 levels less than 1 g/L from the onset of the disease, and $^{18}$F-FDG-PET-CT revealed an unusual bone marrow activity. Therefore, other diagnoses were considered.

To conciliate paraclinical and histopathological findings, a second analysis of the sample was performed. A predominance of lymphocytes over plasma cells was noted, as well as numerous eosinophils, mummified cells and, notably, a few lacunar cells (Reed-Sternberg variants), pathognomonic of nodular sclerosing Hodgkin’s lymphoma (Fig. 4), positive for CD15 and CD30 marking, hence confirming nodular sclerosing Hodgkin’s disease. The final diagnosis was a mediastinal nodular sclerosing Hodgkin’s lymphoma.

The patient was then treated with BEACOPP chemotherapy (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), which is the conventional treatment for stage III and IV of Hodgkin’s lymphoma.

3. Discussion

The differential diagnosis of a thyroid mass is complicated, especially between Riedel’s disease and mediastinal Hodgkin’s disease, as already discussed by Vigouroux et al. in 1993 [18]. However, the differential diagnosis was recently enriched by new data on Riedel’s disease. Indeed, some authors consider the latter as an entity of the IgG4-related disease, described in the early 2000s [13,17]. The etiology of this disease remains unclear. It is characterized by high levels of IgG4 ($>1.35$ g/L).

The diagnosis can also be confirmed by immunolabeling the lesion with an IgG4 antibody (with a ratio IgG4-positive plasma cells/IgG-positive plasma cells greater than 50% or IgG4-positive plasma cells greater than 10 at a strong magnification) [17]. IgG4-related disease is associated with certain inflammatory and fibrosclerosing pseudotumors, likely to reach different tissues: pancreatitis, interstitial nephritis, sclerosing cholangitis and thyroid gland.

The clinical, biological and radiological evolution is favorable under treatment with corticosteroids and is associated with a decrease of IgG4 levels. In the present case, serum IgG4 levels remained within the normal range from the start, which, a priori pleaded against the diagnosis of RT.

Moreover, positron emission tomography is a medical imaging technique that is increasingly used to assess RT extent and treatment efficacy [4]. In the present case, $^{18}$F-FDG-PET-CT revealed mediastinal lesions, as well as a high agent uptake at the

Fig. 4. Reed-Sternberg variant cells (black arrow) were noted, pathognomonic of nodular sclerosing Hodgkin’s lymphoma.
bone marrow, usually observed when the marrow was stimulated because of an inflammatory syndrome, anemia or lymphoma [26], but usually not in case of RT.

The first histological analysis performed on a tissue sample of 1 cm² revealed dense, fibrous tissue dissecting the muscle in the absence of thyroid tissue (Fig. 2). Due to the suggesting clinical aspect and important fibrosis, a diagnosis of Riedel’s disease was first proposed. It should be noted that the closest entity of the disease linked to IgG4 in histopathological terms is lymphoma, characterized by the presence of a majority of infiltrating B cells, detectable if the tissue is not too fibrous, which was the case here.

However, the lymphoid inflammatory response in hyper-IgG4 is mainly composed of T cells. In the present case, it was thus difficult to confirm Hodgkin’s disease, and even more so because Reed-Sternberg cells were sparse in the sample. Reed-Sternberg cells are malignant cells specific of Hodgkin’s disease and of lymphoid origin [17].

The patient thus suffered from a highly fibrogenic Hodgkin’s disease, as indicated above. This type of lymphoma is more frequently found at the mediastinal level. Most affected patients are young women, in whom the disease can be detected by symptoms of compression (cough, dyspnea, chest pain), and in rare cases by a thyroid mass [18,23,25], similar to that observed in patients with Riedel’s disease.

Accurate diagnosis is important because the treatment of these two diseases is very different. Indeed, RT treatment remains highly controversial because of the absence of randomized studies due to the rarity of the disease. Surgery is only performed to free the respiratory system in case of severe tracheal stenosis. Treatment with corticosteroids remains the standard treatment, although there is no consensus on the initial dose or duration of treatment. Tamoxifen alone or in combination with corticosteroids, with a mean dose of 40 mg/day, was proposed because it could inhibit fibrosis. Conversely, the treatment of the lymphoma consists of chemotherapy followed by radiotherapy delivered to the initial tumor bed.

4. Conclusions

The case reported here emphasizes the difficulty of differential diagnosis of a thyroid mass, especially between Riedel’s invasive fibrous thyroiditis, a condition with unknown etiology, perhaps indicating the localization of a more systemic fibrosclerotic disease or a sclerosing form of lymphoma.

The therapeutic outcome of both diseases after treatment with corticosteroids is similar at first, with a decrease in the size of inflammatory tissue and of the fibrosis, which is very confusing. No specific examination that can easily differentiate between both diseases has been reported in the literature. However, serum IgG4 level is a good indicator, and should form part of the tests performed when facing a case of thyroid fibrosis. Finally, as mentioned before, (18)F-FDG-PET-CT be used to estimate the extension of the fibro-inflammatory process, but also to redirect the diagnosis, as other spots can be detected, e.g., of the bones, which are not described in Riedel’s thyroiditis and are consistent with a diagnosis of lymphoma.

Author contribution

P.O. wrote and edited the manuscript.
P.O. and P.M. reviewed the manuscript.
P.O., C.D., E.R. and A.D. contributed to the discussion.
P.O., P.M., F.W., A.D., C.D. and E.R. contributed to the data collection.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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