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Coexistence of Tuberculosis and Malignancy in a Single Lymph Node

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ABSTRACT

The coexistence of tuberculosis and malignancy in the same lymph node is very uncommon. The purpose of this article was to discuss, through our cases, clinical features and treatment options of this condition. We conducted a retrospective study including cases of concomitant tuberculosis and malignancy within the same cervical lymph node treated between 2008 and 2022. The study included ten patients. They received or were receiving treatment for cancer or tuberculosis in seven cases. All patients presented with recurrent or new lymph nodes despite being under treatment. The three remaining patients had no history of cancer or tuberculosis. The histopathological exam confirmed the coexistence of tuberculosis and malignancy within the same lymph node. Histological types of the diagnosed cancers included: laryngeal squamous cell carcinoma, papillary thyroid carcinoma, nasopharyngeal carcinoma, medullary carcinoma of the thyroid gland, Hodgkin lymphoma, non-Hodgkin lymphoma and diffuse large B cell lymphoma. All patients received treatment for tuberculosis and cancer. Average duration of antituberculosis treatment was eight months (6-12). Two patients were dead because septic complication in one case and for pulmonary complication due to miliary tuberculosis in one case. Concomitant tuberculosis and malignancy are possible, especially in countries with high tuberculosis incidence. Therefore, a detailed histopathological examination is required to prevent misdiagnosis. Immunocompromised states related to cancer and its treatments can add the risk of flare-up of a latent infection.

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Introduction

Tuberculosis (TB) is a widespread infectious disease that represents a major health problem and a major cause of morbidity and mortality in the world.

Approximately one-third of the world's population has latent infection with Mycobacterium Tuberculosis [1]. Tunisia represents the third endemic country in the world among high TB burden countries [2].

In 1855, Rokitansky put forward the theory that TB and malignancy cannot exist within the same organ and highlighted a definite antagonism between the two [3].

However, Whartin described for the first time in 1899, the coexistence of cancer and TB within the same lymphadenopathy. This condition is very rare, and only a few cases have been reported in the literature especially in countries with a high incidence of TB [2,4].

The purpose of this article was to discuss, through our cases, clinical features and treatment options of concomitant TB and malignancy within the same cervical lymph node.

Materials and Methods

This is a retrospective, single-centre epidemiological study conducted at the Military Hospital of Tunis in Tunisia from 2008 to 2020. The study includes patients diagnosed with the coexistence of lymph node tuberculosis and malignancy (haemopathy or metastasis of a solid cancer) within the same cervical adenopathy based on histological criteria. Retrospective data was collected from the patients' medical records, including epidemiological data, disease history/discovery circumstances, clinical examination, results of bacteria culture tests, biological and radiological explorations, anatomopathological examination reports, prescribed treatment, and post-treatment evolution.

Patients who did not give consent or who were missing important data, such as anatomopathological report or evolution data, were excluded.

The study was authorized by the Local Committee for the Protection of Individuals (LCPI) of the main military training hospital in Tunis (Tunisia).

Results

The study included ten patients (5 men and 5 women). All patients have been BCG-vaccinated.

Two patients have been diagnosed with cancer first (lymphoma) and were receiving (n=1) or received (n=1) treatment. Four patients received (n=2) or were receiving (n=2) treatment for TB. One patient had a history of cured TB and was being treated for a nasopharyngeal carcinoma.

Table 1: Characteristics of the Reported Cases

Patient	History of Tuberculosis	Initial State at the Time of Diagnosis	Main Complaint	Affected Lymph Node Chains
1	-	_	Chronic dysphonia + dysphagia + weight loss + cervical lymph nodes	II-IV [bilateral]
2	yes [pulmonary]	_	Dysphonia + anemic syndrom + cervical lymph nodes	II-III-V
3	-	_	Cervical lymph nodes + anterior cervical swelling [thyroid] + nocturnal sweat	II-III [bilateral]
4	-	Tuberculous cervical lymphadenitis under treatment [6th month]	Treatment failure [new lymph nodes] + nasal obstruction	II-III
5	yes [pulmonary]	Treatment failure? [new cervical lymph nodes]	Treatment failure? [new cervical lymph nodes]	II-III-IV [bilateral]
6	yes [nodal]	_	Cervical lymph nodes + anterior cervical swelling	III
7	-	Tuberculous cervical lymphadenitis + pulmonary tuberculosis under treatment [5th month]	Treatment failure [new cervical lymph nodes] + anterior cervical swelling	II-III-IV-V
8	-	Hodgkin lymphoma [completed chemo-radiotherapy]	Recurrence of cervical and inguinal lymphadenopathy + hemoptysis	III-IV-supraclavicular-inguinal
9	-	Non-Hodgkin's lymphoma [under chemotherapy]	Nocturnal sweats, hemomptysia, diffuse lymphadenopathy	II-III-IV-V- axillary-inguinal
10	-	_	cervical lymph node	II

The other cases (n=3) were not diagnosed with either cancer or TB.

All patients presented with recurrent or new lymph nodes.

Other symptoms included hoarseness, dysphagia, nosebleed, nasal obstruction, hemoptysis, weight loss and nocturnal sweat.

On physical exam, lymph nodes were mainly located in levels II and III of the neck. They were bilateral in 3 cases.

The tuberculin skin test was performed in five cases and was positive in 3 cases.

Neck ultrasound was practiced in five cases. It showed bilateral well-defined hypoechogenic lymph nodes, with preserved echo structure in two cases. It also showed thyroid nodules classified as EUTIRADS IV and V nodules. Lymph nodes had a thyroid-like appearance in one case. They had areas of necrosis in three cases.

Computed tomography (CT) was performed in 7 cases. It showed necrotic appearing lymph nodes (in 5 cases). It also showed mediastinal nodes in two cases (cases 7,8). One patient had military TB on CT-scan.

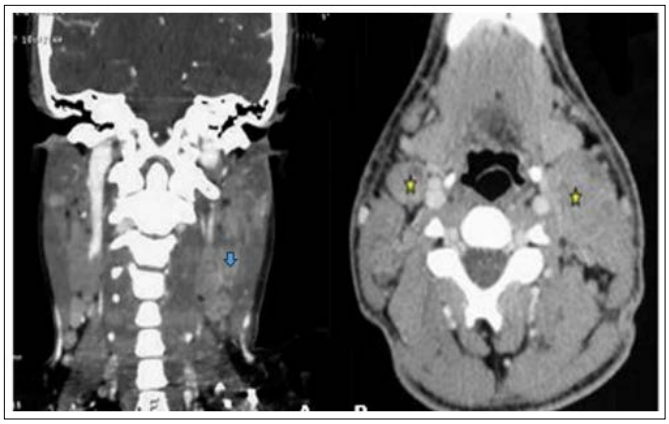

Figure 1:
A. CT scan of the Neck in a Coronal Section showing Multiple Bilateral Cervical Lymphadenopathy (Blue Arrow) in a Patient Receiving Treatment for Lymphoma
B. CT scan of the Neck in an Axial Section showing Bilateral Cervical Lymphadenopathy (Yellow Star) with Areas of Necrosis. The Patient was being Treated for a Nasopharyngeal Carcinoma.

Lymph node aspiration was performed in five cases. She showed lymphoid cells in two cases and caseous necrosis in one case. Bovis tuberculosis was identified on only one case in PCR exam.

Histopathological exam of the swollen node was performed in all cases. The coexistence of TB and malignancy in the same lymph node was confirmed histologically for all patients.

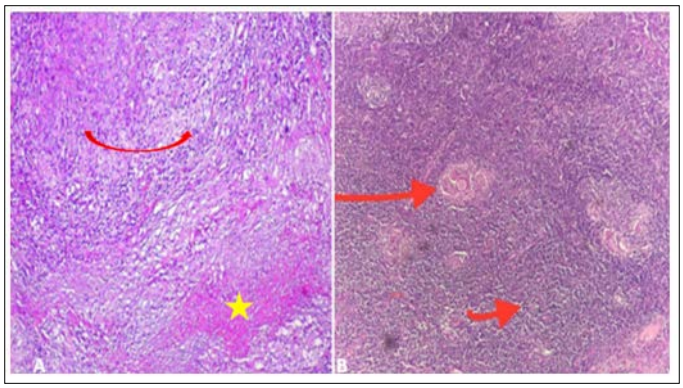

Figure 2: HE*250:
A. Proliferation of Undifferentiated Carcinoma Cells (Yellow Star) with an Epithelioid Granuloma Centered by Caseating Necrosis
B. Reed-Sternberg Cells (Little Red Arrow) and Epithelioid and Gigantocellular Granulomas (Big Red Arrow)

Histological types of the diagnosed cancers included: laryngeal squamous cell carcinoma (SCC) (n=2), papillary thyroid carcinoma (PTC) (n=2), UCNT (n=2), medullary carcinoma of the thyroid gland (n=1), Hodgkin lymphoma (n=1), non-Hodgkin lymphoma (n=1) and diffuse large B cell lymphoma (n=1).

Treatment is detailed in Table 2. It was provided in collaboration with infectious disease specialists and oncologists.

Table 2: Histological Type of Malignancy and Treatment

Patient	Histological Type	Treatment
1	Laryngeal squamous cell carcinoma	Total laryngectomy + LND+RT-CT
2	Laryngeal squamous cell carcinoma	Total laryngectomy
3	Papillary thyroid cancer	Total thyroidectomy+ CND + LND+ RAI
4	Undifferentiated nasopharyngeal carcinoma [UCNT]	Neoadjuvant CT+ concomitant CT-RT
5	Undifferentiated nasopharyngeal carcinoma [UCNT]	Concomitant CT-RT
6	Papillary thyroid cancer	Total thyroidectomy+ CND + LND+ RAI
7	Medullary thyroid carcinoma	Total thyroidectomy+ CND + LND +RT
8	Hodgkin lymphoma	CT-RT
9	Non-Hodgkin lymphoma	CT-RT
10	Diffuse Large B cell lymphoma	CT-RT

CT = Chemotherapy, RT = Radiotherapy, LND = Lateral Neck Dissection, CND= Central Neck Dissection, RAI=Radioactive Iodine

All patients who were not having chemotherapy at the time of diagnosis received a minimally of 15 days of TB treatment before starting chemotherapy (15-30 days).

The patients received combined TB treatment for an average duration of eight months (two months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) (HRZE) quadritherapy and four to eight seven months of heartbeats (HR) bitherapy). Follow-up was based on clinical, biologic and radiologic exams (cervical ultrasound and facial magnetic resonance imaging (MRI). Secondary effects of TB treatment were dominated by voming and/or hematologic disturb in three cases. Chemotherapy was delayed until the biological balance was normalized.

Eight patients were doing fine after treatment. Two patients died during treatment, one of them because of miliary TB with pulmonary and hepatic complications, the second one because of septicemia due to aplasia secondary to chemotherapy (case 9).

Discussion
A complex relationship between TB and malignancy has been highlighted especially in countries with high endemicity for TB [5].

The mutual influence between TB and cancer is not fully understood. Some suggest that the coexistence is purely coincidental. Others propose that cancer cachexia may offer a good nutritional basis for dormant bacteria. Also, cancer may be superimposed on chronic progressive TB [3].

Other authors suggest that chronic immunosuppression may be favorable for the development of simultaneous or secondary existence of both disorders in the same patient [6]. In our study, TB affecting the patient diagnosed with Hodgkin's lymphoma and treated by chemotherapy and allograft can be explained by

the immunodeficiency induced by the tumor and its treatment.

The tumor itself, particularly locally advanced or metastatic tumors may also predispose patients to the reactivation of TB.

TB may play a leading role in carcinogenesis. Physio pathologically, an escape of Mycobacterium Tuberculosis from the immune response with the development of persistent chronic inflammation by producing nitric oxide and oxygen-derived reagents free radicals, oxygen ions, peroxides] may explain this phenomenon. The chronic inflammation with apoptosis inhibition and resulting DNA alterations are responsible for mutations preceding dysplasia and thus carcinogenesis [7].

An average delay of 4 and 11 months in the diagnosis of cancer in TB patients was described [3].

Clinically, TB has similar symptoms to cancer especially hematologic malignancies [4]. Lymph nodes, weight loss, and night sweats can be seen in these two illnesses [4]. In the reported cases of synchronous TB and head and neck cancer, failure while treating TB was the most frequent circumstance of discovery of cancer [8].

In our study, four patients received or were receiving treatment for TB. They presented with recurrent or new lymph nodes. Treatment failure was suspected.

To our knowledge, only two cases of coexistent tubercular lymphadenitis and metastatic nasopharyngeal cells within a cervical lymph node have been reported.

The coexistence of TB and SCC of the upper aerodigestive tract in the same lymph node was first described by Gheriani et al in 2006. So far, only a dozen cases have been reported in the literature. In Squamous cells carcinoma, TB should always be considered, even in non-endemic areas, particularly in elderly patients, mainly due to cancer-induced immune suppression [9].

The coexistence of TB and metastasis of PTC in the same lymph node is also very uncommon.
On imaging, suspecting nodal TB is usually difficult in patients diagnosed with cancer. In fact, TB and malignant tumors share common imaging features. On ultrasound, TB nodes tend to be round hypoechoic lesions and usually show intranodal cystic necrosis and calcification, similarly to metastatic nodal PTC [10]. However, these two pathologies can coexist [3].

Both lymph node TB in the subacute phase and lymph node metastasis have low central absorption and thick and irregular enhancement of the edges on CT-scan [9].

Hodgkin's lymphomas, as well, can show similar features in physical exam, tests and imaging [8].

In our study, ultrasound and CT were not helpful in distinguishing between TB and metastatic nodes. They showed calcification and necrosis which both can be found in the two situations.

Diagnostic efficiency of Fine Needle Aspiration Cytology [FNAC] varies between 46% and 90% and PCR has a sensitivity of 82% and specificity of 100% for detecting TB [10]. Combined FNAC and PCR for detecting Mycobacterium Tuberculosis should be employed in patients treated for cancer every time TB is suspected. In our study, we underwent five lymp node aspiration, two of them were non conclusive. She showed lymphoid cells in two cases and caseous necrosis in one case. PCR was positive in one case detection Bovis tuberculosis.

Quantiferon TB-2G testing is relatively new and often used for extrapulmonary TB. The sensitivity and specificity were shown to be 70–90% and 90–100% [10]. Diagnostic utility of tuberculin skin test is very low in the background of a malignancy because of the underlying immune suppression. However, Tuberculin skin test threshold of 5 mm can be considered as positive for patients with hematological cancer since they have the highest rates of active TB, followed by patients with head and neck cancer. In our study, Tuberculin skin test was performed on 5 patients and was positive in 3 cases [11].

To confirm the diagnosis of a concomitant TB and malignancy, histology remains the most reliable exam; although in some cases, caseating or necrotizing granulomatous lesions typical for TB can also be found in other tumors including Hodgkin lymphoma and non-Hodgkin lymphoma [12]. Moreover, a granulomatous reaction can be seen in SCC against keratin produced by tumor cells [7]. Additionally, the distinction between nasopharyngeal cancer and TB can be difficult since nasopharyngeal cancer can cause a granulomatous response within the peritumoral tissue [13].

Treatment of TB in patients having cancer is not well codified. However, it must always be discussed at a multidisciplinary consultation meeting [11]. In practice, according to Matsuo et al, once a patient has developed TB, anti-TB treatment takes priority, although this depends on the severity of the infection [14]. Chai et al recommended in their study to start anti-TB treatment at least 15 days before anti-cancer treatment. However, in some cases, anti-TB and anti-cancer treatment could be administered simultaneously [15]. It was also demonstrated that only poor performance status, extremely drug-resistant Mycobacterium Tuberculosis and severe organ dysfunction were the basic contraindications for simultaneous treatment with concomitant chemotherapy [16]. Fujita et al. suggested waiting up to two months before initiating anti-cancer treatment while remaining cautious about the impact of this approach on the prognosis and progression of cancer [17]. Hirashima et al concluded in their study that patients with cancer coexisting with active TB could safely receive anti-cancer and anti-TB treatment [16].

Ito et al. recommend surgery of the primary tumor and anti-TB treatment before lymph node dissection in order to avoid the spread of TB infection [18]. Furthermore, treatment options for cancer including chemotherapy, radiotherapy, immunotherapy and targeted therapy, could lead to drug interactions and worsen the side effects of anti-TB drugs, including skin rashes, hepatitis, kidney failure and lymphopenia [15,17]. In our study, for patients who had chemotherapy, a minimal of 15-day deadline was respected before initiating anticancer treatment.

According to Skogberg et al. extra-pulmonary localization of tuberculosis is more frequent in immunocompromised patients, and may thus mimic a tumor, partly explaining the delay in diagnosis and treatment [19]. Furst D et al. also support this theory, explaining why tuberculosis disease is discovered at an advanced stage [20].

Response to treatment also varied between authors. Adzic et al. reported a 90% good response rate, with only one death due to miliary tuberculosis [21]. Good tolerance was also reported by

Paluku in two series reporting an association of tuberculosis and acute leukemia [22].

In our study, side effects of tuberculosis treatment were dominated by vomiting and haematological disorders in three cases. Chemotherapy was delayed until biological equilibrium was normalized. Two patients died during treatment, due to miliary tuberculosis in one case and sepsis due to aplasia secondary to chemotherapy.

Limitations

Several paraclinical examinations such as cytopuncture and ultrasound were not systematic in our series, which caused a delay in diagnosis and management.

Conclusion

The coexistence of neoplasia and TB infection within the same lymphadenopathy can mislead and delay the diagnosis and treatment of one or the other disease. Atypical response to treatment must reconsidered the diagnosis. The definitive diagnosis is based on information obtained from clinical history, physical examination, laboratory and imaging findings. In some patients, a revised biopsy of the involved tissue should be considered.

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