Lymph node tuberculosis after melanoma treatment – sometimes the patient is lucky

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Abstract
Tuberculosis (TB) is considered a pulmonary disease that can however disseminate to other organs through hematogenous dissemination following primary TB infection. Evolution of the disease can either be precocious, before healing of the primary infection, or late after primary infection, due to reactivation of initial lesions usually because of simultaneous immunosuppressive factors such as diabetes, renal disease, hepatic disease or different type of immunosuppressing treatments. Rare cases when tuberculosis and cancer are diagnosed at the same time create diagnostic difficulties and therapeutic challenges. We present the case of an asymptomatic 52-year-old female that was diagnosed “by chance, at the right moment” with a form of skin melanoma on the right forearm, for which she received a rather well tolerated cytostatic treatment. At the end of this treatment, she was also investigated for a breast mass that proved to be benign; however, enlarged lymph nodes were discovered in the right armpit were discovered upon further investigation. One of the lymph nodes was surgically removed, as a “standard” evaluation for lymphadenopathies [5].

Keywords: lymph node tuberculosis, melanoma, immunosuppression, chemotherapy.

Introduction
Large epidemiological studies acknowledge that close to one-third of the population become infected with Mycobacterium tuberculosis. Reactivation in extrapulmonary sites occurs in approximately 10–15% of these cases, generally posing a diagnostic issue, as these cases do not present any signs of active pulmonary disease [1].

Most authors consider tuberculosis (TB) a pulmonary disease, although it can affect a number of other organs. Thus, extrarespiratory TB designates localizations that do not involve lungs, pleura, intrathoracic lymph nodes and the larynx. Lymph node involvement is the most common form of extrapulmonary tuberculosis. Human immunodeficiency virus (HIV) infection and other immunocompromising conditions are predisposing factors for lymph node TB, their rise in incidence and co-occurrence with TB also influencing the incidence [2, 3].

Extrarespiratory TB occurs due to the hematogenous dissemination that occurs in primary infection [3]. Evolution of the disease can either occur before healing of the primary infection, or late after this event, due to reactivation of initial lesions. M. tuberculosis and, to a lesser degree, M. bovis have previously been identified as the most common causes of lymph node TB [2].

Many other diseases can target lymph nodes, ranging from infectious diseases and benign reactive enlargements to manifestations of underlying malignancies. Over 75% of all lymphadenopathies only affect one station, with more than 50% found at the head and neck areas. Cervical lymph nodes are involved more often than the other lymphatic regions [4, 5].

Infections are the most common cause, while supraclavicular lymphadenopathies are associated with malignancy. Assessing lymph node characteristics continues to be of special importance even in today’s medicine. The detection of lymph node metastasis in cancer patients has to be accurate in order to establish curative solutions and to assess prognosis [4, 5].

TB is one of the main benign causes of lymphadenopathies in adults and children from tropical areas. Complete medical history and a thorough physical examination are mandatory for accurate diagnosis; a battery of laboratory tests is also necessary, combined with imaging and tissue sampling. Tissue diagnosis by fine-needle aspiration or excisional biopsy is the “gold standard” evaluation for lymphadenopathies [5].

We present the case of a middle-aged female patient, previously diagnosed with skin cancer, who underwent chemotherapy and later presented with axillary adenoven
pathy of unknown origin, supposedly metastatic, which pathology revealed to be extrapulmonary TB.

Informed consent was obtained for each procedure and all investigatory and treatment protocols were in accordance with current international ethical regulations.

Case presentation

A 52-year-old female patient, without significant personal or family history, was admitted to the Clinic of Dermatology, in June 2015, with the intent of removing unaesthetic facial moles. Upon closer inspection of another mole, of about 1.7 cm diameter, on her right forearm, the physician decided that it needed surgical excision as it presented irregular edges. She had no other symptoms and her laboratory results were normal. Surgery was performed and recovery was excellent, without scars.

Her pathology exams for all the moles removed was received after one month. The moles on the face had normal structure, however, the one on the forearm presented the structure of a skin melanoma, diagnosis also confirmed by further immunohistochemistry.

Her detailed histopathological exam evidenced a Clark level IV description, as invasion into the reticular dermis was present, Breslow’s depth 1.4 mm, and mitotic rate was 4/mm². Other ulceration, tumor regression, perineural invasion or satellite nodules were not identified on the sections examined.

For immunohistochemistry, we used the Ventana BenchMark GX automated system, ultraview Universal DAB Detection kit with primary antibodies: anti-S100, anti-melanosome, P21, anti-Ki67 and the following clones anti-S100 (polyclonal), HMB45, DCS-60.2 and 30-9.

Immunohistochemistry evidenced HMB45 and S100 diffuse positive tumor cells, including deep intradermal components. We identified p21 positive nuclei in almost 90% of tumor cells. In addition, focal Ki67 was positive in almost 15% of tumor cells nuclei, including deep intradermal component.

Following positive diagnosis, she received six cycles of cytostatic treatment with Cisplatin 100 mg associated with Dacarbazine 600 mg and Vinblastine 10 mg between July and December 2015, which the patient tolerated with no significant side effects.

During treatment course, she received regular laboratory exams at the start of every treatment period. At four months from the start of her therapy, the patient presented a decrease of her hemoglobin value from 14 g/dL to 10.62 g/dL and a short increase of her creatinine value from 0.52 mg/dL to 1.18 mg/dL and of blood urea from 26 mg/dL to 63 mg/dL.

An abdominal and a breast ultrasound exams were also performed during this treatment. The abdominal ultrasound exam was in normal parameters.

The patient had discovered after self-examination a particular tumor mass in her right breast. A breast ultrasound exam was performed in October 2015, which evidenced suspect right axillary lymph nodes of approximately 3 cm with intense vascularization and a 2 cm tumor mass in her right breast. Consequently, the patient was scheduled for a mammography during the same month. This time, the mammography did not evidenced a tumor, only calcifications and fibrotic structures confined to a small region of the breast, responsible of the tumor-like aspect. Enlarged axillary lymph nodes with modified structure were also discovered in right armpit region.

She agreed to admission to the Surgical Department during December 2015 for removal of one of the lymph nodes from her right armpit region. At admission, the patient was asymptomatic and had finished her cytostatic treatment for melanoma. Her laboratory exams only showed a slightly decreased hemoglobin value of 10.5 mg/dL and a low white cell count (2600/mL).

Her chest radiography did not evidenced any active lesions or other sequelae from chronic respiratory diseases.

The microscopic exam of the surgically removed lymph node evidenced large areas of caseation and epithelioid follicles (Figures 1–3), with gigantic multinuclear Langhans cells (Figures 4–6).

Follicles contained large areas of necrosis, with significant inflammatory changes and cellular inconsistencies. Langhans cells were predominantly visible at the periphery of the tuberculous nodules.

The aspects were suggestive for a specific granulomatous lesion (TB lesion).

Based on pathological exam result, we established the diagnosis of axillary lymph node tuberculosis.

Figure 1 – Tuberculous follicle showing necrosis and inflammatory changes. Hematoxylin–Eosin (HE) staining, ×100.

Figure 2 – Tuberculous follicle with central necrosis and caseous material. HE staining, ×100.
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Figure 3 – Large area of necrosis, with caseum and a large, multinucleate cell. HE staining, ×200.

Figure 4 – Detail of a multinucleate Langhans cell at the periphery of a TB follicle. HE staining, ×200.

Figure 5 – Large follicular structure, with central necrosis and dispersed caseum. A large, multinucleate Langhans cell can be observed at its periphery. HE staining, ×200.

Figure 6 – Detail showing a Langhans cell within a tuberculous follicle. HE staining, ×200.

Because of her recent melanoma diagnosis and treatment, we further submitted the patient to a thoracic, abdominal and pelvic region computed tomography (CT) scan in January 2016. CT scan of thorax revealed a small calcified nodule in the left superior lobe (Figures 1 and 2), and some linear fibrosis in the left upper lobe and right inferior lobe, without enlargement of other lymph nodes in the mediastinum. Other enlarged (up to 0.97 cm in diameter) axillary lymph nodes were also seen in right armpit region (Figure 7, A and B).

Figure 7 – (A and B) CT scan. Small calcified nodule in left upper lobe. Enlarged right axillary lymph nodes. (mediastinal window).
Serological studies for HIV and VDRL (venereal disease research laboratory) were negative.

The patient continued anti-TB treatment according to The National Program for Tuberculosis Control in Romania that follows the guidelines of the World Health Organization (WHO). As per the directly observed treatment, short-course (DOTS) – regimen I of anti-TB treatment, we administered the association of Isoniazid, Rifampin, Pyrazinamide and Ethambutol in the first two months, continuing with Isoniazid and Rifampin three times a week for the following nine.

During the first five months of the treatment, the evolution was good, without any side effects related to medication. She continues to be monitored for melanoma symptoms and no signs of lab abnormalities or other local or general symptoms have been observed.

Discussion

Melanoma

Melanoma, a cancer that derives from melanocytes, is 20 times more common in whites than in African Americans. It represents 1% of all skin cancers; however, it is responsible for the majority of skin cancer related deaths especially because of its great metastatic rate to the lymph nodes, lungs or brain.

Melanoma is less common than basal cell and squamous cell skin cancers and it can develop anywhere. Preferred locations are on the chest and back in the case of men and most commonly the lower limbs of women. Other common sites for melanomas are the neck and face, and most commonly the lower limbs of women. Other common sites for melanomas are the neck and face, and most commonly the lower limbs of women.

The staging system most often used for melanoma is the American Joint Commission on Cancer (AJCC) TNM system. Biopsies of skin and areas other than the skin (e.g., lymph nodes) may be needed in some cases [7, 8].

Our patient had a skin melanoma Clark level IV, classified as pT2a pNx after detailed histopathological exam that evidenced invasion into the reticular dermis, Breslow’s depth was 1.4 mm, and mitotic rate was 4/mm². We did not identify other ulcerations, tumor regression, perineural invasion or satellite nodules on the examined sections. Lymph nodes evaluated with ultrasound exams at the time of diagnosis had no signs of enlargement or modified structure. Patient lactate dehydrogenase (LDH) was normal at diagnosis and during treatment course. Her prognosis was very good and chemotherapy was initiated after two weeks.

For our patient, the oncological treatment included cycles of Cisplatin, Dacarbazine and Vinblastine according to the guidelines, with each period of treatment followed by a rest period to give the body time to recover. Each cycle of chemotherapy typically lasted for a few weeks. Patient did not experience severe side effects and did not require immunotherapy drugs such as interferon-alpha and/or interleukin-2. The future follow-up schedule will include physical exams every six to 12 months for several years, as she was diagnosed “by chance” with an early-stage melanoma that was removed completely.

Lymphadenopathy

Lymphadenopathy translates to an abnormal increase in size, consistency and number of lymph nodes. All lymphadenopathies commend complete evaluation of the patient and any palpable lymph node should be monitored for location, size, consistency, adherence to underlying tissue and tegumentary aspect [5]. Literature states that, in general, multiplicity, matting and caseation are features of tuberculous lymphadenitis; these aspects lack however specificity and sensitivity. Enlarged lymph nodes are usually hard and adherent to the underlying structures or the overlying skin when associated with malignancies [6].

Imaging (ultrasonography, magnetic resonance imaging and computed tomography) is vital for assessing lymph node characteristics [7].

Our patient had no personal or family history of tuberculosis, nor had any other chronic diseases before her melanoma diagnosis. All the lymph nodes that were evaluated by physical and ultrasound exam at the time of the initial melanoma diagnosis were in normal limits as size and structure.

The mass found by the patient during self-examination occurred during chemotherapy, therefore subsequent discovery of the lymph node enlargement was suspected as malignant at first. The suspect right axillary lymph nodes were of maximum 3 cm in diameter with intense vascularization. Mammography excluded a breast tumor. Enlarged axillary lymph nodes with modified structure were also seen in right arm region. Smaller size lymphadenopathies were observed in the left arm region. Physical exam of the right arm region, performed prior to surgery, described several painless, enlarged lymph nodes, well delineated, firm and mobile. Corroborating this with the lack of symptoms but given her recent history of cancer, the next decision was to surgically remove one of the lymph nodes from the right armpit to perform histopathological and immunohistochemical exams in order to better differentiate the cause of lymphadenopathies.

The first microscopic exam was suggestive for a specific granulomatous lesion. Differential diagnosis for tuberculous lymphadenitis includes reactive hyperplasia, lymphoma and other causes of infection: Mycobacteria other than tuberculosis (MOTT), fungi, and toxoplasmosis. In addition, sarcoidosis, metastases of a carcinoma and HIV-related lymphadenopathy need to be excluded.

Lymph node tuberculosis

Lymph nodes are a preferred site of involvement for extrapulmonary TB, followed by pleural effusion and other organs [8–11].

Extrapulmonary tuberculosis prevalence is between 15% to 20% of all cases of TB in endemic countries and accounts for more than 50% cases in immunocompromised individuals [12–14]. Extra-respiratory tuberculosis has a very low risk of infectivity [15].

The inflammatory process that develops during TB affects the lymph node groups in an order linked to the entrance point, be it primary or secondary infection. According to some authors, TB cervical lymphadenitis would be the most common or among the most common
forms of extrapulmonary tuberculosis. Favorite locations are anterior cervical and posterior lymph nodes, and supraclavicular lymph nodes. The following lymph node groups are the axillary, the mesenteric and the peri-pancreatic ones (most commonly affected groups in the abdominal lymph nodes TB), then inguinal, epitrochlear, mediastinal and the intramammary groups [16–18].

Tuberculous lymphadenitis is a local manifestation of the systemic disease [19]. It can develop during primary TB infection or, later in life, because of reactivation of dormant M. tuberculosis or through direct extension from another TB affected organ. Primary infection occurs after initial exposure to bacilli, when very small inhaled droplets containing M. tuberculosis pass the mucociliary defense system of the bronchial tree up to terminal alveoli of lungs. The infection can further disseminate to regional lymph nodes and may continue to spread via the lymphatic system to other nodes or could reach the blood stream and spread to other organs (hematogenous dissemination). The first filter lymph nodes that are affected are hilar, mediastinal, paratracheal lymph and supraclavicular [20–23].

For our female patient, the thorax CT scan revealed a small, calcified nodule, in the left superior lobe, which we assumed as a mark of her previous primary TB infection. That was probably the moment when M. tuberculosis reached extrathoracic lymph nodes because of lymphatic or hematogenous spread. The reactivation of dormant bacilli in the axillary lymph nodes was probably due to immunodepression caused by recent chemotherapy for melanoma. No signs of active pulmonary TB were seen at the moment of lymph node TB diagnosis. Our patient was “by chance” prematurely discovered with lymph node tuberculosis. The aspect of the lymph nodes was similar to stage 1; this could explain her lack of symptoms at diagnosis and her favorable evolution under treatment.

For TB diagnosis, we generally used mycobacterial culture as a “gold standard” but in extrapulmonary TB, its low positivity rate represents a challenge. In the reviewed literature, polymerase chain reaction (PCR) has been shown to have sensitivity ranging from 75 to 100% and specificity of 99 to 100% [24, 25] and can be used as the gold standard for the detection of M. tuberculosis complex organisms in the causation of lymphadenitis.

Also, biopsy or surgery can offer tissue for diagnosis [8]. Our patient displayed a wide range of histological alterations specific to TB infection, with large areas of caseous material, necrosis and large multinucleate cells aggregated with macrophages, fibroblasts and lymphocytes, forming granulomas.

**Overlapping cancer and tuberculosis**

Rare cases when TB and cancer are diagnosed at the same time or one after another create diagnostic difficulties and therapeutic challenges. Kaplan et al. [26] studied 201 cancer patients with concomitant TB. In their study, TB was most prevalent in patients with Hodgkin’s disease, lung cancer, lymphosarcoma, and reticulum cell sarcoma, and not so frequent in patients with carcinoma of the colon, bladder, uterus, breast, prostate, and kidney [26].

Cancer patients may suffer reactivation of their TB during their treatment because of immunosuppression induced by the disease or by the treatment. M. tuberculosis can exist in a state of microbial persistence within the macrophage of the primary formed TB granulomas for the lifetime of the individual in immunocompetent individuals. Conditions that influence host immunity can reactivate dormant bacilli to cause endogenous reinfection [27, 28]. Changes in cancer therapy and increased survival may influence tuberculosis risk, especially in endemic countries. Prophylaxis anti-TB treatment could be recommended for patients with hematological malignancies or head and neck cancer and latent TB infection [29, 30]. Treating latent TB to prevent reactivation due to the immunosuppressive state associated with cancer and chemotherapy may lead to unnecessary side effects associated with anti-TB treatment; however, most authors recommend to start cancer patients on anti-TB treatment before initiating chemotherapy [31].

Our patient was not evaluated for latent TB in the moment of melanoma diagnosis or during her treatment. Even so, with no history of personal and familial TB, no symptoms suggestive for any sign of tuberculosis, a normal chest X-ray and almost normal blood exams, she developed reactivation of the bacilli that persisted within her right axillary lymph nodes. The simultaneous occurrence of tuberculosis and cancer lead to diagnostic and therapeutic challenges.

**Conclusions**

Our case showed that immunodepression induced by chemotherapy might lead to reactivation of viable M. tuberculosis within the macrophage of the granulomas, especially in endemic countries. In these countries, prophylaxis anti-TB treatment should be recommended for patients receiving chemotherapy for cancer. Cancer and TB presenting simultaneously or one after the other creates clinical and histopathological difficulties for differential diagnosis and for therapeutic decisions.

**Conflict of interests**

The authors declare that they have no conflict of interests.

**Author contribution**

Cristina Călărașu and Isabela Siloşi equally contributed to the manuscript and share main authorship.

**Informed consent**

Written informed consent was obtained from the patient for this case report, procedures and any accompanying images.

**References**


