Clinical Case Report

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Incidental finding of non-Hodgkin's lymphoma in a patient affected by castration-sensitive prostate cancer

A case report

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Abstract

Rationale: This article describes the case of a patient with 2 simultaneous malignant diseases: Follicular lymphoma and 'castration sensitive prostate cancer. Patients with multiple cancers are not easy to manage and it is difficult to find the appropriate approach and resources to use with them. We focused our attention on how to choose the correct strategy to face 2 different neoplasms and control the adverse reactions related to the corresponding treatments.

Patient concerns: We present a case of a 71-year-old man who came to us complaining about an abnormal difficulty in urinating associated with an interrupted flow and excessive urination at night. Clinical examination detected multiple enlarged superior and inferior diaphragmatic lymph nodes.

Diagnosis: Prostate biopsy revealed an acinar adenocarcinoma (Gleason 4+3, Grade group 3). Clinical staging by bone scan was negative but computed tomography scan (CT) detected multiple enlarged superior and inferior diaphragmatic, and inguinal lymph nodes. This type of lymph node involvement pattern is unusual for an acinar adenocarcinoma prostate cancer therefore we suspected the simultaneous presence of a lymphatic neoplasm. Fluorodeoxyglucose positron emission tomography scan. The exam showed one of the left inguinal lymph nodes had the highest standardized uptake value (13.0) so a biopsy was taken. The sample analysis confirmed the diagnosis of a follicular non-Hodgkin lymphoma of Grade 3a.

Interventions: We used a multidisciplinary clinical approach based on Rituximab+CHOP administered every 21 days. Simultaneously, the patient underwent androgen deprivation therapy with triptorelin monthly and bicalutamide administered just during the first month of treatment. When we obtained a complete response for the lymphoma, the patient continued the therapy with Rituximab once every 2 months for the next 2 years. Then we added volumetric modulated arc therapy (VMAT) radiotherapy with simultaneous integrated boost (SIB) to androgen deprivation therapy for the duration of 1 month.

Outcomes: After 1 year and 6 months since the conclusion of therapy for prostate cancer and Follicular lymphoma, patient's conditions are good and he is in complete remission for both diseases. Gut toxicity is reduced with a mean number of 2 to 3 discharges daily and an increased body weight.

Lessons: The presence of diffuse lymphadenopathy and urinary symptoms in the same patients must induce the suspect of 2 contemporary cancer diseases. Parallel treatments of follicular lymphoma and prostate cancer should consider the increased risk of severe adverse effects related to the treatment and their management. We describe our therapeutic strategy to highlight the importance to balance benefits and disadvantages to get the best possible response and maintain a good quality of life in this complex setting.

Abbreviations: BCL-2 = B-cell lymphoma 2, BCL-6 = B cell lymphoma 6, CT = computed tomography, FL = follicular lymphoma, OS = overall survival, PFS = progression free survival, PSA = prostate specific antigen.

Keywords: chronic enteritis, multiple primary neoplasms, non-Hodgkin lymphoma, pelvic radiotherapy, prostate cancer

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Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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1. Introduction

Follicular lymphoma is the most prevalent subtype of low grade lymphoma, making up 30% of all non-Hodgkin lymphomas with an overall survival (OS) of 72% to 77% at 5 years from diagnosis.[1] It is a B-cell lymphoma characterized by tumor cells that appear in a circular, or clump like, pattern. It is associated with the overexpression of Bcl-2 protein which plays a key role to avoid the programmed cell death (apoptosis). The most known mutation responsible for the upregulation of Bcl-2 is the translocation t (14;18).[2] As a consequence of t(14;18), Bcl-2 is regulated by the immunoglobulin (Ig) heavy chain gene promoter. Because the heavy chain gene is highly expressed normally, this event causes the increase of Bcl-2 gene transcription and translation. Being Bcl-2 an antiapoptotic molecule, the consequence is the increment of cell replication cycles which leads to the accumulation of mutations necessary for the neoplastic transformation.[3] Rarely, BCL-6 rearrangement is seen together with BCL-2 and C-MYC. Prostate cancer is the most frequently diagnosed malignant cancer among men with more than 50 years.[4] The OS is 91% at 5 years from diagnosis and is growing constantly. The etiology is multifactorial and is the result of a complex interaction between genetic (familiarity) and environmental factors (high fat diet, excessive caloric intake, environmental carcinogens). The risk to develop the disease is doubled for the first-degree relatives of patients affected by this pathology. If 2 or more relatives are affected, the risk increases by 5 to 11 times.

2. Case report

We report the case of a 71-year-old man who was diagnosed with prostate cancer in March 2016. Comorbidities referred were: generalized epilepsy treated with phenobarbital, Dupuytren' s disease, diverticular bowel disease, Peyronie's disease, and diffuse cerebral atrophy due to previous episodes of cerebral ischemia. Furthermore, he had a positive family history for prostate cancer, breast cancer, and pulmonary cancer. Histology revealed an acinar adenocarcinoma (Gleason 4+3, Grade group 3). Clinical staging by bone scan was negative but computed tomography scan (CT) detected multiple enlarged superior and inferior diaphragmatic and inguinal lymph nodes. Specifically, the preaortic and lateral aortic groups were those with larger diameter (6.5 cm). This type of lymph node involvement pattern is unusual for an acinar adenocarcinoma prostate cancer therefore we suspected the simultaneous presence of a lymphatic neoplasm and decided to do a fluorodeoxyglucose positron emission tomography scan. The exam showed one of the left inguinal lymph nodes had the highest standardized uptake value (13.0) so a biopsy was taken. The sample analysis confirmed the diagnosis of a follicular non-Hodgkin lymphoma of Grade 3a. The molecular evaluation with nested PCR was conducted on blood sample and bone marrow biopsy detected the translocation t(14;18) in June 2016. Clinical staging, according to Ann Arbor criteria, was conclusive for a IVA Stage. Considering the clinical findings (age >60years, maximal diameter of lymph node >6 cm, bone marrow violated), the patient was allocated in the prognostic high risk group according to the Follicular Lymphoma International Prognostic Index 2 (FLIPI-2) with a 5-year PFS of 18.8%. Multiparametric-magnetic resonance imaging (mp-MRI) of prostate disease was performed in April 2016. It showed the evidence of areas with a notable PI-RADS score (4), specifically the peripheral posteromedial apical area of the right lobe and the peripheral posteromedial and lateral area of the left lobe (Fig. 1). There were also initial signs of capsular invasion in the same areas of the left lobe. We decided to treat the most aggressive condition firstly, thus improving the overall status of the patient and obtaining a better response of the second disease to the next therapy. Rituximab (375 mg /m^2 IV) +CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1,4 mg/m^2, prednisolone 40 mg/m^2) was administered every 21 days from June 2016 to October 2016. Hematologic toxicity G3 neutropenia was treated with filgrastim (300 μg daily) and G2 anemia with erythropoietin (50 UI/kg, 3 times per week). Simultaneously the patient underwent androgen deprivation therapy with triptorelin (3.75 mg monthly) and bicalutamide (150 mg daily administered just during the first month of treatment) since July 2016. At the beginning of treatment, the PSA value was 7.930 ng/mL. At the

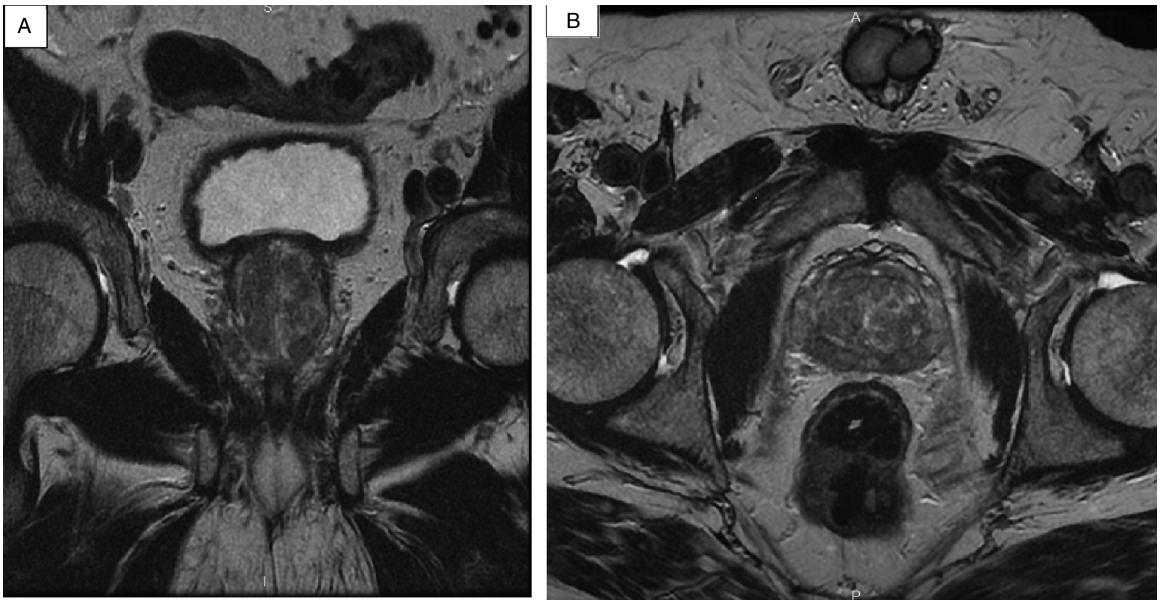

Figure 1. MRI showing prostatic lesions, (A) coronal view, (B)axial view. MRI = magnetic resonance imaging.

first follow up (after 6 cycles of R-CHOP) we recorded a complete response (RC) of the Follicular lymphoma and a significant decrease of PSA value (0.081 ng/mL). The patient continued the therapy with Rituximab (1400 mg/m^2 sc) once every 2 months for the next 2 years. Then we added volumetric modulated arc therapy (VMAT) radiotherapy with simultaneous integrated boost (SIB) to androgen deprivation therapy in March 2017 for the duration of 1 month. The radiotherapy targets were pelvic lymph nodes (total dose = 54Gy), prostate gland (total dose = 64.5 Gy) and seminal vescicles (Total dose = 72 Gy). The patient suffered of mild diarrhea as adverse effect during the treatment. In January 2018, after 8 months from the conclusion of radiotherapy, the patient who was still under therapy with triptorelin (3.75 mg every 28 days) and rituximab (5 cycles by May to January), developed chronic diarrhea associated with the following abdominal symptoms and signs: burning pain, tenesmus, watery stools. Due to the malabsorption, the patient lost 9 kg in 2 months. Therefore, we chosen to interrupt the administration of rituximab in order to treat the diarrhea properly. The patient engaged a diet regime based on the elimination of vegetables and legumes. He started a treatment with mesalazine (800 mg, 3 times daily for 6 weeks) and probiotics. On February 2018, a biopsy of the colorectal mucosa was conducted. Histology revealed a moderate atrophy of the epithelium with reduction of goblet cells number. In addition, there were signs of edema, congestion and an abundant chronic and acute inflammatory infiltrate associated with diffuse cryptitis. All these findings confirmed the diagnosis of ulcerative colitis. After three months of treatment we managed to obtain a complete resolution of symptoms and patient gained 7 Kg. Rituximab was readminstered in May 2018. At the last follow up (April 2018), after 1 year and 6 months from the conclusion of chemotherapy (CHOP) for the follicular lymphoma and 1 year from radiotherapy for the prostate cancer, he maintains a complete remission (CR). The sequence of treatments and the entity of adverse effects are summarized in Table 1.

3. Discussion

Case reports that document unfortunate patients with more than one malignant neoplasm are rare and many questions about their pathogenesis have still no answer. A large number of elements influencing carcinogenesis have been implicated in such cases including chemotherapy for the original malignancy, prolonged history of heavy smoking and exposure to other environmental carcinogens, ageing and underlying genetic alterations. Within the last few years, many studies have focused on the association between *BRCA2* gene polymorphisms and cancer risk, including breast cancer, ovarian cancer, non-Hodgkin lymphoma, prostate cancer. Li et al[5] reported a meta-analysis to prove the association between *BRCA2* rs144848 polymorphism and cancer risk. A total of 40 relevant studies from 30 publications including 34,911 cases and 48,329 controls were included in the final meta-analysis. Among them, 22 studies focused on breast cancer, 7 on ovarian cancer, 5 on non-Hodgkin lymphoma, and the remaining six studies examined various other cancers. The meta-analysis showed that there were significant associations between the rs144848 polymorphism and cancer risk in all genetic models. Stratifying by cancer type, the rs144848 polymorphism was associated with non-Hodgkin lymphoma so it might be a low penetrate risk factor enhancing carcinogenesis in breast cancer. Cooper et al[6] obtained the genotype of 1121 patients with prostate cancer for 36 risk alleles known to be significantly associated with prostate cancer and established their relationships with other malignancies in prostate cancer probands and their first-degree relatives. In this work, the probands with a family history of multiple myeloma and non-Hodgkin's disease were significantly more likely to be carriers of SNP (single nucleotide polymorphisms) rs 12621278 (2q31, P.04) and rs 6465657 (7q21, P.02). They concluded that certain alleles associated with prostate cancer susceptibility might be associated with an increased or a decreased risk of other malignancies in prostate cancer probands and their first-degree relatives. Carbone et al[7] described 2 cases of lymph nodal in situ FL complicated by the association with nonlymphoid neoplasms. In one case, in situ FL was discovered incidentally on a biopsy performed for an unexplained cervical lymphadenopathy 6 months after the resection of a carotid body paraganglioma. In the other case, in situ FL was detected incidentally during surgery for radical resection of prostatic carcinoma. From a clinical point of view, an important challenge is to understand whether the occurrence of an in situ lymphoma might give any prognostic information when it is associated with other type of malignancies. Major open questions should face the following problems: how to approach and monitor these patients who also have a risk of progression to overt lymphoma and to find out if the association of in situ FL with concurrent incidental neoplasia is related to immune suppression or to previous treatment.

Mandal et al[8] reported the history of a 67-year-old male presented with generalized lymphadenopathy. Lymph node biopsy was suggestive of follicular lymphoma (FL). Bone marrow (BM) aspiration and trephine biopsy were positive. Serum prostate specific antigen (PSA) and Tru-cut biopsy of prostate were suggestive of adenocarcinoma prostate (ACP). Bilateral orchiectomy was performed together with bicalutamide followed by six cycles of R-CHOP. Positron emission tomography (PET) showed complete remission. Di Meglio et al[9] described the challenging case of a 56-year-old man whose pathological assessment of pelvic lymph nodes removed during radical retropubic prostatectomy for a high-grade prostatic neoplasm revealed Hodgkin lymphoma. The disease was treated with the EBVD regimen (epirubicin 35 mg/m^2, bleomycin 10.000 U/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2). Bicalutamide (150 mg/die) was prescribed for the persistence of elevated PSA. Then the patient underwent pelvic irradiation and finally reached RC for both diseases. Our patient had an acute severe enteritis after 8 months by radiotherapy and chemotherapy so we searched on PubMed to look for possible explanations. The irradiation of pelvic organs can cause mucositis in the bowel. Hernandez Moreno et al[10] assessed the prevalence, risk factors, and complications of chronic radiation enteritis in patients who had received pelvic radiotherapy. The study included 100 patients,

Table 1

History of patient's treatment.

Treatment	Approximate duration in months (number of cycles)	Adverse events
R-CHOP	6 months	G3 asthenia G3 neutropenia
Bicalutamide	1 month	Breast swelling
triptorelin	16 months	Erectile dysfunction Tiredness and weakness (fatigue)
Radiotherapy	1 month	G2 asthenia G3 diarrhea

84%males, median age 72.3 years. Chronic radiation enteritis was found in 20% of the patients, most of them G1 (45%). Furthermore,10% had lost>5 kg of weight, 3% had been hospitalized due to diarrhea or bowel obstruction, and 11% had changed their diet, mainly by removing vegetables, legumes, and pastry. Male gender, age, previous acute radiation enteritis, and chemotherapy were associated with chronic enteritis, but only chemotherapy remained independently related to the bowel toxicity after multivariate analysis.

Goldner et al[11] used endoscopy before radiotherapy to assess whether previous diseases might more frequently result in early or late toxic effects after radiotherapy. The most commonly developed diseases were: hemorroides (35%) polyps (24%) and diverticula (13%). No correlation between pre-existing intestinal disease and radiotherapy toxicity was found.

Delobel et al[12] carefully analyzed factors that determine a rectal toxicity after radiotherapy for a prostate cancer. They identified dose escalation and moderate hypofractionation as the factors that cause the late rectal toxicity and concluded that an approach combined with IMRT (intensity modulated radiation therapy) and IGRT (image-guided radiation therapy) markedly decrease acute and late rectal toxicity.

4. Conclusions

Although literature contains significant experiences about cases of multiple malignancies in the same patient, many issues still reclaim answers and clarifications due to the low number of cases. Firstly, the risk of synchronous primary tumors is frequently correlated to a mixture of genetic and environmental factors but none of these is able alone to justify univocally the onset of multiple cancers in the same patient. Secondly, more studies are required not only to solve the complex interaction between these elements but also to define a correct clinical approach to face the adverse effects elicited by overlapping therapies. Our case, in fact, showed the importance of decision making for patients with 2 types of cancer and the higher risk to develop important and dramatic adverse events if physicians do not balance benefits and disadvantage to treat one disease before the other properly.

Author contributions

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