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Diagnostic Delay in Oncology: A Case Report of Metastatic Seminoma

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Key Words
Diagnostic delay · Metastatic seminoma · Cryptorchidism · Acute bleeding complication · Cisplatin-based chemotherapy · Complete pathological response

Abstract
Germ cell tumours are the most common malignancy among young men; cryptorchidism is a possible risk factor for the development of testicular cancer. Psycho-oncology studies indicate that diagnostic delay can often be explained by different social conditions and that symptoms worsened under lack of appropriate treatment can lead to an urgent admission to the hospital. Nevertheless, germ cell tumours are considered curable malignancies even in advanced stages since the introduction of a chemotherapy regimen based on bleomycin, etoposide and cisplatin. Cell lines derived from germ cell tumours are sensitive to cisplatin-based treatment more than other solid cancers, which is reflected in the good clinical response. We report an unusual manifestation of malignancy in an adult man presenting with a metastatic seminoma of the left testicle. The large ulcerate and necrotic mass suggested a secondary infection from a tumour site. The patient reported surgical orchiopexy for left cryptorchidism in his childhood. Despite worsening of physical features, he had not sought help at the hospital for social reasons. The patient achieved complete clinical remission after receiving standard chemotherapy, and a good objective response of the primitive mass was clearly visible. Complete response was persistent at the 30-month clinical follow-up. The chemotherapy administration was later complicated by acute haemorrage in the site of the primitive tumour that needed urgent surgical management; in addition to this, the artificial graft material was rejected and the arterial prosthesis had to be removed.
This case report can be considered for epidemiologic contribute, for clinical relevance despite diagnostic delay and for psycho-oncology studies.

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Case Report

In April 2008, a 38-year-old man presented with a solid mass, which had been rapidly growing for 3 months, involving the left testicle and the whole inguinal region. His clinical history was relevant for left cryptorchidism in childhood. He had undergone surgical orchiopexy for this condition at the age of 9 years. No more clinically significant diseases or pathologies were reported. The reason why the patient had not presented to hospital earlier, despite the atypical overgrowth and worsening of physical features, was his social condition; the patient delayed seeking the advice of a healthcare professional after self-discovery of the symptoms because he feared to be dismissed from his occupation.

The most relevant finding on physical examination was a large ulcerated and necrotic mass extending over the left testicular and scrotal structures with detached margins of neoplastic tissue. The proliferating lesion suggested the macroscopic appearance of a secondary infection induced by a tumour (fig. 1). At clinical examination, no tumour markers were found in laboratory tests; in particular, levels of lactic dehydrogenase, beta-human chorionic gonadotropin, and alpha-fetoprotein were not elevated. Computed tomography scan documented a massive vascularized growth inside the whole iliac site involving cutaneous and muscular tissues, the left testicular and scrotum structures, from the bladder surface to the leg junction, with 27 cm as the largest diameter. Multiple enlarged left iliac and bilateral inguinal nodes were detected. Complete radiologic staging revealed lung metastases but no other sites of disease (fig. 2). Surgical biopsy of the lesion was performed and the patient was diagnosed with metastatic seminoma (cT4cN1M1a). Immunohistochemical staining was positive for placental alkaline phosphatase and CD117/c-kit and negative for CD30/BerH2, MNF116 and S-100 protein.

The patient underwent combined bleomycin, etoposide and cisplatin (BEP) standard chemotherapy; the number of cycles of chemotherapy was scheduled according to specific prognostic factors of the International Germ Cell Cancer Collaborative Group Consensus Classification (IGCCCG) criteria. After 4 courses of treatment he achieved complete clinical remission; the deep excavated lesion had considerably decreased in size, its surface was cleaned. As a good objective response following the second course of chemotherapy was clearly obtained, a surgical biopsy of the previous tumour site was repeated and pathology report did not find any tumour cells (fig. 3). Evaluation by computed tomography and fluorodeoxyglucose-PET scan did not reveal any residual disease on the former site of injury (fig. 4).

The completion of chemotherapy treatment was characterized by a serious and acute vascular complication in the site of the primitive neoplasm : 8 days after the fourth course of therapy, the patient suddenly had to be hospitalized because of a massive acute haemorrhage due to wide erosion of the left common femoral artery surface with consequent subacute ischaemia of the left leg. The adverse event needed urgent surgical management, and re-canalizing of the femoral artery was performed by vascular prosthesis placement. Despite the seriousness of the adverse event, bleeding was rapidly stopped and arterial vascularization was completely achieved. Unfortunately, 2 months later the artificial graft material was rejected and the femoral prosthesis had to be removed. As the healing process of the former necrotic tumour was ongoing and scar tissue was permanently being developed, no further vascular prosthesis needed to be implanted. Henceforward neither acute nor chronic bleeding sequels occurred.

Another complication of chemotherapy was asymptomatic pulmonary infection following the last administration of treatment; pulmonary fibrosis induced by bleomycin was excluded since the patient received concomitant antibiotic medication establishing complete radiological resolution of documented pneumonia. Additional treatment with radiotherapy was not planned in order to avoid any wound-healing complications in the growing granulation tissue.

Today the patient is alive and disease-free after 32 months of clinical observation. A normal sexual performance is reported.

Discussion

Germ cell tumours (GCTs), mainly presenting as testicular cancer, are relatively rare neoplasms that account for 0.8% of all cancers in males. However, GCTs are the most common malignancy among 15- to 44-year-old men [1]. The aetiology of testicular

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malignancy is unknown but epidemiological studies indicate a relationship between intrauterine and perinatal testicular development and undescended testes [2, 3], the latter being a common congenital anomaly among males. It is well documented that men with a history of cryptorchidism have a higher likelihood of developing testicular GCTs. The probability is 1:2,000 [4] and is increased 32-fold compared to the general population. The risk is highest with intra-abdominal testicles, five times higher than for inguinal cryptorchidism [5].

Since ectopic position of the testes is considered a risk factor for the development of testicular cancer and infertility, early diagnosis and treatment are essential. In men with unilateral cryptorchidism, even if in the majority of cases the malignancy is on the affected side [4], the influence of the surgical correction before puberty on the risk of malignancy is a contentious issue [6]. From literature we know that the risk of malignancy is almost twice as high in boys operated after the age of 13 years only [7]. Since ectopic position of the testis is considered a risk factor for the development of testicular cancer, early diagnosis and treatment are essential. Treatment can be surgical (orchiopexy) or hormone-based and its purpose is to reduce the risk of malignancy and/or infertility [8].

A second important aspect of the case presentation concerns the diagnostic delay: qualitative psycho-oncological studies have documented that some patients responded to disease symptoms by using self-medication and disclosing their discovery of symptoms to their family [9]. Problems with access to healthcare professionals and patients' social responsibilities acted as barriers to prompt help-seeking. Epidemiological data showed that lower social class was associated with a more advanced clinical stage of cancer, and with a higher probability of urgent admission to the hospital for a newly diagnosed disease. Delay in seeking care did not, however, seem to explain the social class differences for disease stage [10].

In addition, GCTs should be considered curable malignancies, even in the advanced stage, since the introduction of cisplatin-based chemotherapy [11] that leads to remission of over 80% of metastatic diseases. The gold standard regimen for metastatic testicular GCTs is BEP; the treatment options are based on pathology (seminoma or nonseminoma) and prognostic criteria of the international classification (degree of elevation of serum tumour markers and presence of visceral metastases) [12]. As a first-line treatment, 3 cycles of BEP should be used in low-risk metastatic nonseminomatous GCTs whereas 4 cycles of BEP are mandatory in high-risk nonseminomatous cancers. The surgical resection of all residual metastatic masses is mandatory after the normalization of serum tumour markers in nonseminoma patients. The cure rates after chemotherapy and surgery are about 90 and 50% in low-risk and high-risk patients, respectively [13]. No other chemotherapy regimen has proven superior efficacy. While almost all other solid cancers in adults are incurable once they have spread beyond their primary site, GCTs are more sensitive to cisplatin-based treatment according to the good clinical response [14]. Earlier findings from literature suggest that a reduced repair capacity might contribute to cisplatin hypersensitivity of testicular tumour cells even if the specific DNA damage has not been defined. Ongoing studies are investigating the formation and repair mechanism of action of intrastrand and interstrand crosslinks induced by cisplatin [15].

This clinical case indicates that despite diagnostic delay due to personal reasons, this metastatic CGT has been successfully managed with appropriate treatment. Our

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experience testifies to excellent results obtained by chemotherapy in advanced seminoma patients. The hypersensitivity of CGT cells to cisplatin-based chemotherapy can facilitate further investigation in order to establish the biologic principles at the bases of formation and repair of intrastrand crosslinks induced by cisplatin on DNA.

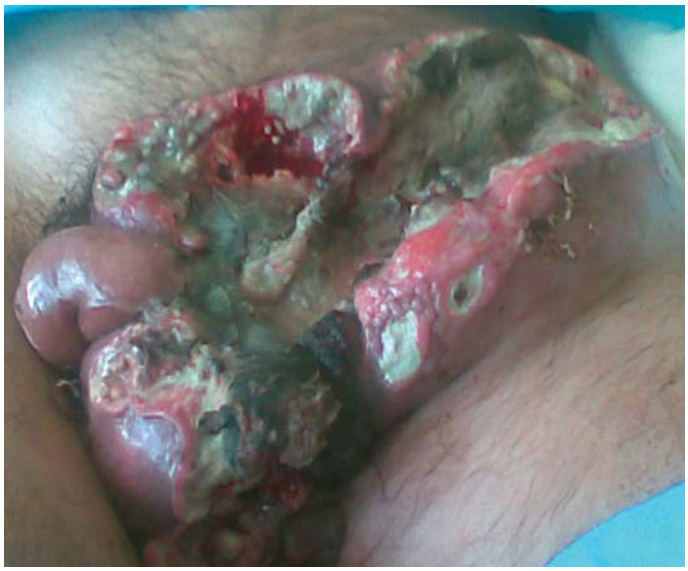

Fig. 1. Ulcerate and necrotic mass suggesting a secondary infection induced by a tumour.

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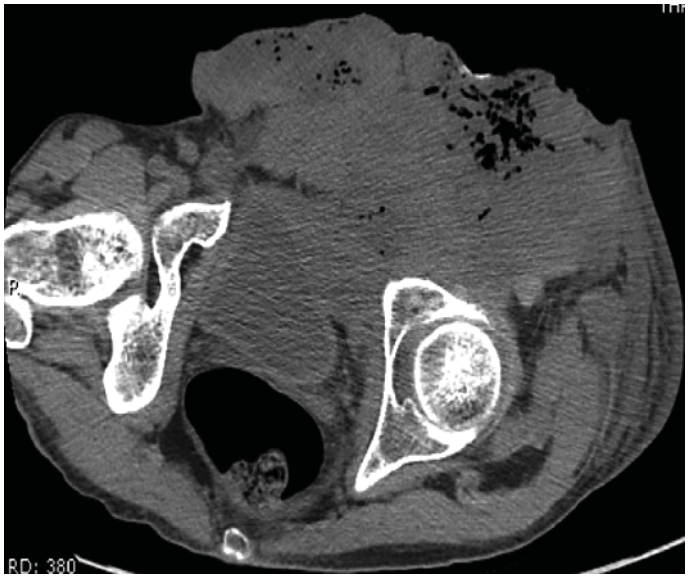

Fig. 2. CT imaging of the massive vascularized growth throughout the iliac area, involving cutaneous and muscular tissues of the left testicle.

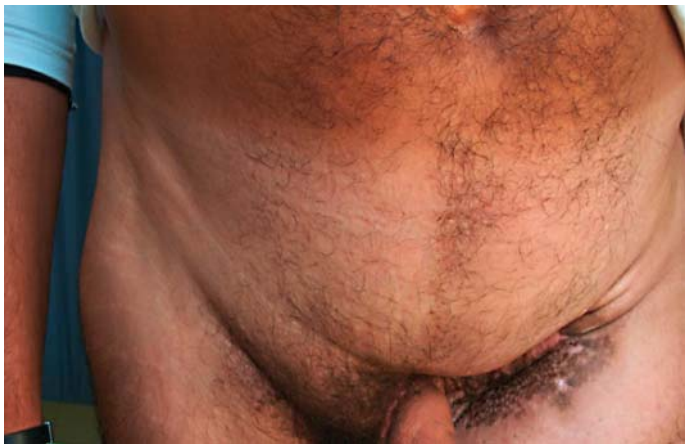

Fig. 3. After completion of chemotherapy, the patient achieved complete clinical remission; the deep excavated lesion had considerably decreased in size, and its surface was cleaned.

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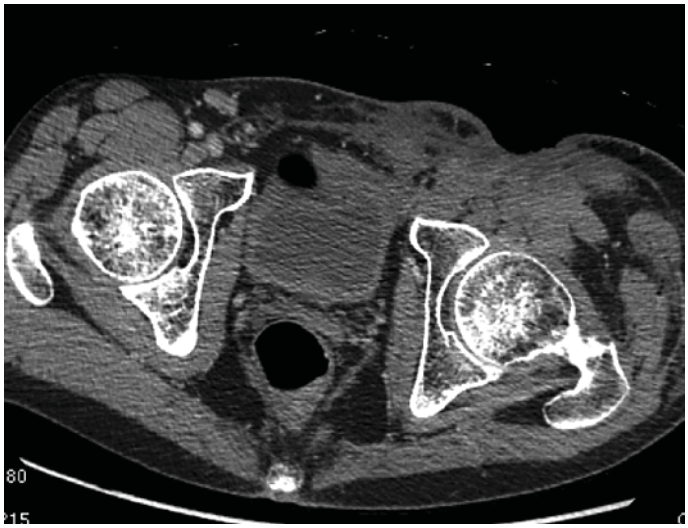

Fig. 4. CT imaging of the clinical response.

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