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Case Report

Contribution of Pathology to Radiological Staging of Testicular Teratocarcinoma

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Abstract

Staging of cancer assumes that all known lesions share the same pathology. While is this true for most cases, it is estimated that up to 16% of "metastases" do differ histologically and almost all harbour evolutionary changes in molecular biology as a result of dedifferentiation or epithelial-stromal interactions. But also tumor heterogeneity can cause differences in metastatic pattern where, for example, one part metastasizes while the other part remains local.

We illustrate this phenomenon by a case of a 39 years old male with testicular cancer and suspicious retroperitoneal lymph nodes. Staging was completed with histology and immunohistochemistry of primary cancer and lymph nodes. Biopsy was performed with special attention to the quality of the sample, i.e. up to 300 mg, providing enough tissue to establish a reliable diagnosis. In this patient, the primary tumor constituted a seminoma testis with only 5% of adenocarcinoma from teratocarcinoma. In the lymph nodes, only the adenocarcinoma part was found.

The case illustrates not only the difference in synchronous cancer lesions from the primary but also explains the phenomenon why late recurrences from a seminomatous testicular cancer turns into teratocarcinoma. Further, it shows that every lesion outside the locoregional area of a cancer should be analyzed histologically, immunohistochemically and, if possible, by molecular biology to complete diagnosis.

Keywords: Testicular cancer, pathology, staging, biopsy, CT-scan, seminoma, teratocarcinoma

Introduction

The incidence of testicular tumors is only 1% of malignancies in man [1]. More than 90% of these cancers originate from germ cells and divided into seminomas and non-seminomas. These types occur about equally. Many testicular cancers contain both seminoma and non-seminoma cells. These mixed germ cell tumors, accounting for 40-45% of all, are best treated as non-seminomas because they grow and spread like non-seminomas. The mixed germ cell tumors contain teratoma, embryonal carcinoma, yolk sac, and syncytiotrophoblasts. A teratocarcinoma is composed of undifferentiated stem cells and their more differentiated derivatives. The stem cells of teratocarcinomas may differentiate into embryonic tissues which are derived from all the three germ layers on one hand and into extra-embryonic cells on the other. Although teratomas are common, a malignant transformation is an uncommon occurrence and it highlights the need for its early recognition, as it is resistant to current chemotherapeutic regimens.

Successful treatments rely on correct diagnoses and the golden standard in oncology is histology of the disease. Nevertheless, a substantial part of contemporary diagnoses is based on assumptions. For example, staging assumes that all suspect lesions share the same pathology. When staging relies on PET-CT scan, the easiest interpretation is that all lesions share a common origin and behave identically. Statistically this reasonable but, in several cases, not all metastatic lesions share the same primary or might dedifferentiate from one primary. Literature shows that between 2% and 15.8% of all cancer patients have multiple primary cancers [2]. Therapies based on insufficient or wrong diagnosis are bound to fail and endanger patient's life, quality of life, and life

expectancy. One way to maximize diagnosis is to acquire tissue from all possible sites that don't fit into the loco-regional extension path of the primary and that can have an impact on treatment decisions. Another reason to sample more sites is the importance of molecular biology where quality of the tissue sample counts [3]. Quality can be characterized as: enough tissue to comply both with histology and molecular biology, representative or pure, and fresh so that all types of multiplatform or multiomic tests can be offered.

Difference in pathology might come from dedifferentiation, stroma factors, synchronous metastatic diseases, or complex oncogenetic processes such as can be found in mixed germ cell cancers. Dedifferentiation is a common reason for so-called "mixed responses". Synchronous disease is a statistical reality, that happens when prevalent cancers occur simultaneously. In some cancers, such as ovarian cancer, metastatic disease might come from different primary sites [4]. Almost all types of histologically different synchronous tumors are already described in a mono setting [5].

Testicular cancer is notoriously known for synchronous cancers [6] and multiple variations of mixed germ-line tumors are a reason for sampling, in particular for retroperitoneal lymph nodes [7] even in the absence of serum tumor markers. Subclinical nodal metastasis might be the cause of later recurrences [8,9], with considerable symptomatology [10]. Mixed germ cell tumors are less radiosensitive and should be recognized before radiotherapy.

In this case, we illustrate how correct diagnosis can be achieved through appropriate imaging and transdermal macrobiopsy technology. More, these innovative diagnostic tools provide us the opportunity to even discover biological behavior that never has been described before. It unravels the earlier observation of a seminoma of the testis that reappears in a metastatic setting as a teratocarcinoma, illustrating that in-situ multiple phenotypic appearances of teratocarcinoma in one primary can also behave biologically different when it comes to metastasis.

Case

A 39-year-old patient presented to his family doctor because of pain in the left testis. The clinical examination confirmed a painful left testis. No pathological lymph nodes inguinal were palpable. The ultrasound showed a suspicious testicular tumor on the left. In the external CT examination no further abnormalities could be observed, except for three pathologically enlarged lymph nodes immediately below the renal pedicle on the left side of the para-aorta (Figure 1). No evidence of lung metastases. No intra-abdominal metastasis. The serum tumor markers alfa-fetoprotein, CEA, and hCG were negative (normal).

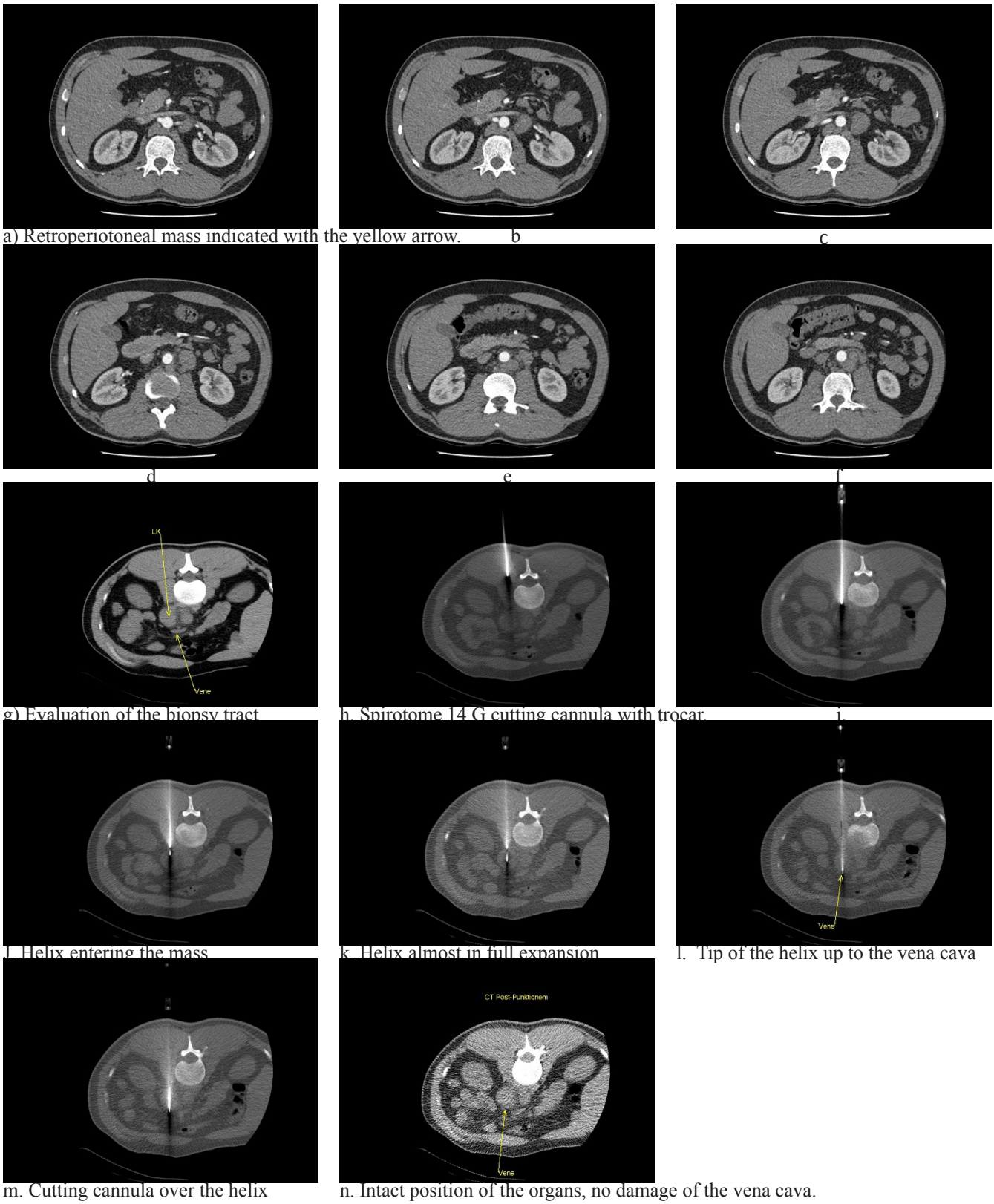
An inguinal ablation of the left testis was performed on May 30, 2018 and disclosed: Seminoma of the left testis - pT1 L0 V0 Pn0 R0 S0 with suspect lymphoid metastasis according to Lugano stage 2b. Microscopically (Figure 2), the tumor showed testicular tubules with partially widened basement membrane and hyaline obliteration of the tubules, and in some areas partly regular epithelium. The basal membrane epithelium region showed round to oval, moderately hyperchromatic nuclei and vacuoles containing bright cytoplasm in the form of tubular intraepithelial neoplasia. The macroscopically described tumor shows a lymphoid stroma, infiltrating narrow close to each other lying tubular tumor cell associations consisting of large tumor cells with round hyperchromatic moderately pleomorphic nuclei and loosely structured cytoplasm, in agreement with a previous frozen section: tissue image of a seminoma. The margins are tumor-free. The epididymis and the spermatic cord are also tumor-free. No lymphovascular tumor invasion, no perineural tumor infiltration. Immunohistochemically, the frozen section diagnosis of a seminoma can be confirmed. The tumor cells are strongly positive for OCT-4, PLAP and CD117 (Fig 4) and negative for EMA. In conclusion, the result of histology and immunohistochemistry proves a classic seminoma with testicular tissue partly atrophic and in places showing hyaline decayed tubules, and in some sections a histological picture of a tubular intraepithelial neoplasia (TIN), TNM pT1 pNx L0 V0 Pn0 R0 S0 with size of 0.9 x 0.6 x 0.4 cm.

Decision of the multidisciplinary tumor conference requested a histological clarification of the enlarged retroperitoneal lymph nodes.

On 19.06.2018 CT-controlled biopsy by means of a 14 G Spirotome (Bioncise NV, Belgium) was made (Figure 1). Histology (Figure 3): CT-guided lymph node puncture shows atypical intestinal glands in fibrosing connective tissue adjacent to lymphatic tissue, according to clinical data from the left paraaortic origin. Infiltrates of a seminoma do not show up. It shows instead well differentiated intestinal glands as they could appear in a teratocarcinoma. The described glands are negative regarding CD30, CD117 and CK7, positive towards CK20 and CDX2. Based on the present immunohistochemical result and the morphology, the finding would be compatible with a well-differentiated adenocarcinoma of the lower gastrointestinal tract (colon / rectum); in terms of differential diagnosis it could also be a metastasis of a well-differentiated teratocarcinoma. Because also neural or cartilaginous tissue was found, we would assume a teratoma here. Whether it is a primary retroperitoneal teratoma or a metastasis cannot be conclusively clarified histomorphologically.

Immunohistochemistry of the primary tumor and metastasis revealed similar data (Figure 4).

After comparison of the testis lesion with the retroperitoneal lesion: this is undoubtedly a retroperitoneal lymph node metastasis of a primary mixed germ cell tumor, with predominantly (95%) from a classic seminoma and only a tiny (5%) proportion of a postpubertal teratoma that constitutes the metastasized the teratoma component.



a) Retroperiotoneal mass indicated with the yellow arrow. b c

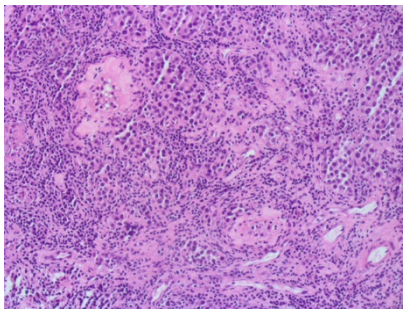
d e f

g) Evaluation of the biopsy tract h. Spirotome 14 G cutting cannula with trocar i.

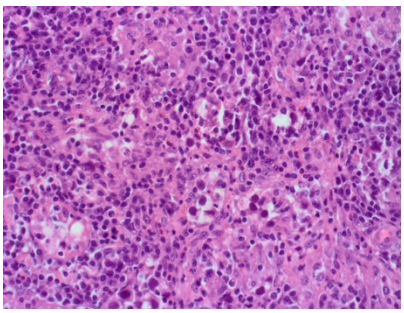
l. Helix entering the mass k. Helix almost in full expansion l. Tip of the helix up to the vena cava

m. Cutting cannula over the helix n. Intact position of the organs, no damage of the vena cava.

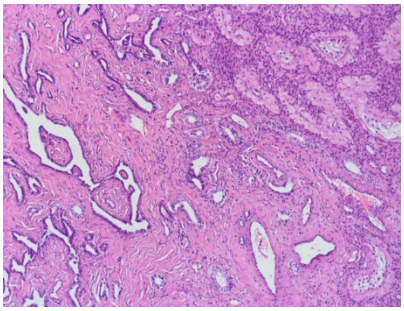
Figure 1: Spirotome procedure under CT-guidance. The Spirotome (Bioncise NV) is a helical biopsy instrument that generates tissue specimen up to 300 mg in a direct and frontal way.



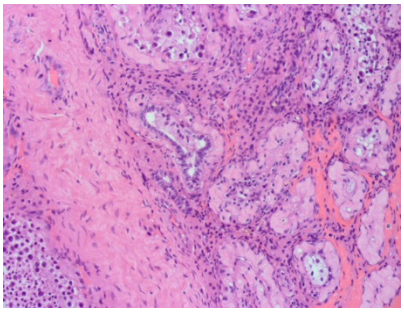
Seminoma 20X: with seminoma cells (pink circle) and atypical ducti (green circle).



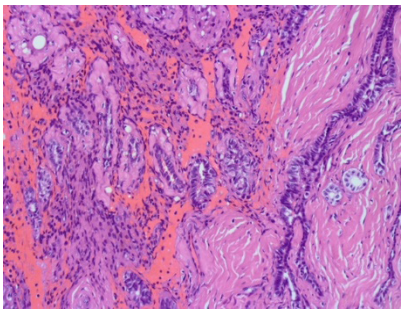
Seminoma 40X.



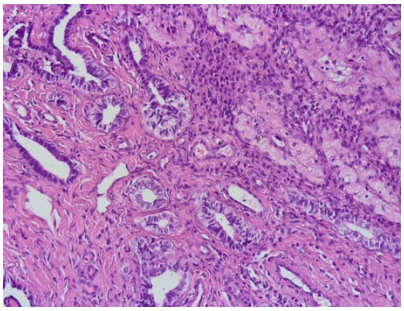
Seminoma - Teratoma 10X with adenoid glands adjacent to the rete testis.



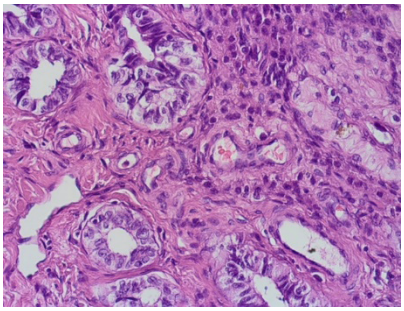
Seminoma-Teratoma 20X.



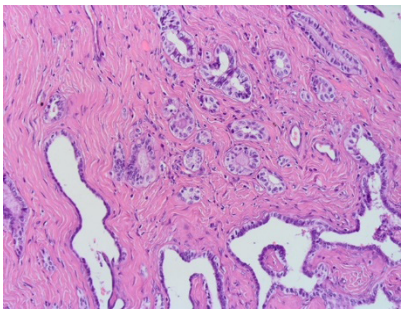
Seminoma-Teratoma 20X1.



Seminoma-Teratoma 20X2.

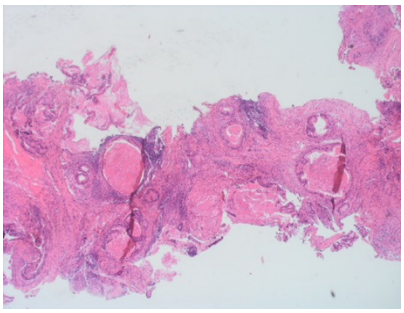


Seminoma-Teratoma 40X.

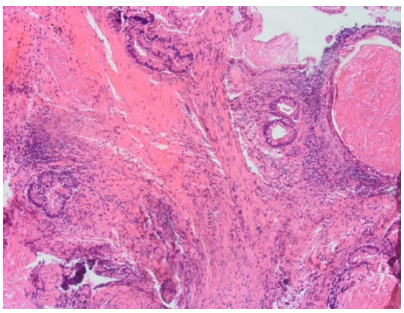


Teratoma 20X.

Figure 2: Histology of testis lesion.

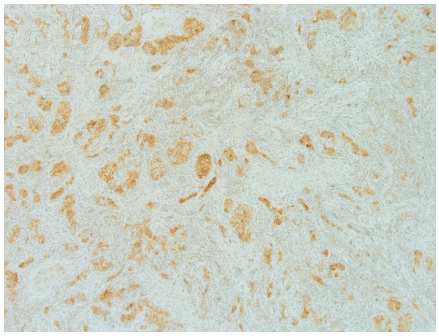


a) Macrobiopsy paraaortic lymph node Teratocarcinoma.

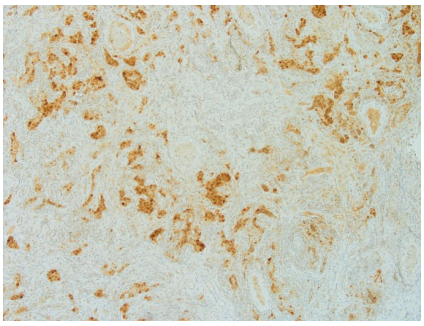


b) Teratocarcinoma lymph node 20X: In circle: well differentiated intestinal glands with globets (colon type epithelium).

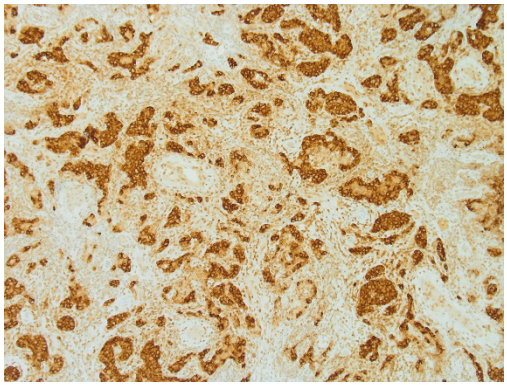
Figure 3: Histology of lymph node lesion.



a) CD 117 immunohistochemistry.



b) OCT-4 immunohistochemistry.



c) PLAP immunohistochemistry.

Figure 4: Immunohistochemical tests.

Gastroscopy on 06.07.2018 investigated the pars descendens of the duodenum. Esophagus: The gastroesophageal junction is at 36 cm from the row of teeth, the diaphragmatic hiatus at 38 cm. In the distal esophagus a single blotchy, reddish, flat mucosal defect. The changes extend to 35 cm from the row of teeth. Stomach: In the antrum of the ventriculi, the mucous membrane of the entire circumference is diffusely red. Duodenum: Unremarkable conditions in the viewed area of the duodenum. Diagnosis: reflux esophagitis. Mucosal aortic antrum. biopsies. HCP test negative.

Colonoscopy 09-07-2018: Findings: Normal digital palpation. We could see up to 10 cm in the terminal ileum. The withdrawal time was 6 min. Condition of colon cleansing (BBPS): 9. Normal wall and mucous membrane conditions in the viewed areas.

Discussion

The observation that non-seminoma testis cancer can recur many years after a seminoma primary cancer has been enigmatic in the past. The reported case of a seminoma that recurs as a teratocarcinoma contrasts with the traditional hypothesis that development of testis cancer is straightforward either being seminoma or non-seminoma. There is now evidence that the oncogenesis is more complicated with consequences for diagnosis and therapy.

New medical technology, such as PET-CT scanning and macrobiopsies under medical imaging, have created opportunities that can study suspicious lesions in a confident way. CT-scan is the preferred way to navigate transdermal biopsy tools and previous clinical research has shown that tru-cut biopsies seldom obtain a complete histological and molecular biology diagnosis. In addition, tru-cut devices are spring powered with inherent dangers towards delicate tissues in the neighborhood such as larger blood vessels. Newer biopsy instruments are designed to harvest high

quality tissue: enough material, pure, and fresh [11]. Also, the comfort to the patient has been substantially improved. They are not powered and completely controlled during the procedure [12]. The case under discussion illustrates that superior diagnostic tools can detect disease in a way that never has been seen before and explains why enigmatic behavior of a cancer can be explained through looking at the early carcinogenic processes, even when they are considered metastatic at the time of diagnosis.

The case illustrates also that some cancers, such as testicular cancer, need elaborated diagnosis to fully understand the disease in an individual. This diagnosis can have great importance for the right treatment, treatment outcome, and to avoid severe symptomatic complications in later stage. In addition, it completes our knowledge of mutational behavior of germ cells [13].

In an era of personalized medicine, oncology has seen a tremendous difference between individual to individual and statistical assumptions that metastatic cancers are alike must be reconsidered. New tools provide opportunities to individualize care much more on biological behavior of cancer cells at different locations.

Conclusion

In conclusion, this is a first description and evidence of synchronous metastases, originating from one primary, with differences in histology, in one individual. It explains why late recurrences of seminomatous cancer can turn into non-seminomatous teratocarcinoma. The case illustrates the importance of quality tissue acquisition through safe transdermal biopsies in the diagnostic work-up together with medical imaging, including PET-CT scan. Macrobiopsy with histology, immunohistochemistry, and molecular biology are mandatory in the staging of testicular cancer since locations at different metastatic sites harbor variations in type of cancer with consequences for optimal treatment. The clinical information can be unique and adds to our understanding of carcinogenesis.

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