

Renal sinus pseudolymphoma in a patient with multiple carcinomas: a case report and a brief review of the literature

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Summary. The term pseudolymphoma refers to a heterogeneous group of benign reactive T-cell or B-cell lymphoproliferative processes of diverse causes that simulate lymphoma clinically and histologically but usually undergo spontaneous remission. Its pathogenesis is still unclear. The prognosis is good although some evidence suggests that pseudolymphoma may progress to lymphoma. Pseudolymphoma of the urinary tract is extremely rare. We herein report a case of pseudolymphoma of the renal sinus in a 70-year-old man, associated with a high grade urothelial carcinoma of the bladder and to a prostatic adenocarcinoma (Gleason score 6). A brief review of the literature is included. The kidney showed a well-defined, whitish soft mass which involved the renal sinus. Microscopically, the lesion of the renal sinus consisted of a proliferation of small to medium size lymphocytes (CD20 positive and Bcl-2 negative) sometimes arranged in hyperplastic follicular structures. The diagnosis was confirmed by molecular studies which showed an oligopolyclonal IgH rearrangement. To the best of our knowledge, this is the second case of pseudolymphoma with a complete molecular characterization ever described in the renal sinus and the first one associated with multiple urogenital carcinomas.

Key words: Pseudolymphoma, Renal sinus, Multiple malignant tumors

Introduction

Pseudolymphoma (PL) is a benign disorder of lymphoid cells, characterized by the formation of follicles with an active germinal center (Hayashi et al.,

2011), which must be differentiated from a low grade lymphoma. Unlike lymphomas, pseudolymphomas usually undergo spontaneous remission. Pseudolymphoma may arise in response to a wide variety of foreign antigens, but most of them are idiopathic. The causes include drugs (Crowson and Magro, 1995), allergens, arthropod bites, infections (Borreliosis, Herpes virus, Leishmania) (Flaig and Rupec, 2007) and tumors. Cases of pseudo-lymphoma have been reported in the gastrointestinal tract (Torigian et al., 2001), lung (Abbondanzo et al., 2000), skin (Arai et al., 2005), orbit (Terada, 2011), salivary glands, tongue, tonsils, larynx, thyroid (Mizukami et al., 1996), pancreas (Nakashiro et al., 1991), liver (Sato et al., 2006; Takahashi et al., 2006; Zen et al., 2010) and kidney (Teranishi et al., 2003). Pseudolymphoma of the urinary tract is extremely rare and that one involving the renal pelvis has been described only once (Teranishi et al., 2003), with little information regarding its clinicopathological features. We report a case of pseudolymphoma of the renal sinus associated with a bladder high grade urothelial carcinoma and to a prostatic adenocarcinoma with a brief review of the literature. To the best of our knowledge, this is the second case of pseudolymphoma of the renal sinus (Teranishi et al., 2003), the first case associated with multiple urogenital carcinomas and with a complete molecular characterization.

Materials and methods

Case report

A 70-year-old man presented to the Siena University Hospital with the onset of haematuria, back pain and malaise. Personal and family past medical history was unremarkable. He showed no abnormal physical findings, including lymphadenopathy. Laboratory examinations results were within reference range comprising blood cell counts, biochemical and renal

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function tests. Urine cytology presented papillary aggregates that were suspicious for malignancy. Abdominal ultrasonography demonstrated a hypoechoic lesion of 50 mm of diameter in the left renal sinus with a peripheral ring-like enhancement, suggestive of metastatic tumour or lymphoproliferative disorder. On abdominal computed tomography (CT), a low density area of 50 mm of diameter, enhanced in early arterial phase, was present. The bladder showed a lesion of 15 mm of diameter in the right wall. Other organs, including regional or para-aortic lymph nodes, displayed no abnormal findings. Cystoprostatectomy with nephroureterectomy was performed. The patient is well ten months after surgery.

Methods

The surgical specimens consisted of left kidney, ureter, perinephric adipose tissue, bladder, prostate and retroperitoneal lymph nodes. Representative samples were collected, fixed in 10% buffered formalin and embedded in paraffin. From each block, tissue sections (4 μ m thick) were obtained and stained with hematoxylin-eosin. Immunohistochemical stainings were performed using the Ultravision Detection System Anti-Polyvalent HRP (LabVision, Fremont, CA, USA, Bio-Optica) and diaminobenzidine (DAB, Dako) as chromogen. We performed immunoperoxidase staining for: CD20, CD3, CD4, CD8, CD5, CD30, CD79a, CD138, Bcl-2, kappa and lambda light chains. PCR was applied to investigate the arrangement of the

immunoglobulin heavy chain genes with DNA templates obtained from the paraffin-embedded specimens. Four to eight 20 μ m thick sections were cut from formalin-fixed, paraffin-embedded tissue blocks. These sections were deparaffinized, digested and DNA further purified. The purified DNA samples were tested for their B-cell IGH clonality using the BIOMED-2 primers, according to the BIOMED-2 protocol (van Dongen et al., 2003). The post-PCR products were visualized by capillary electrophoresis on the ABI PRISM 3100 genetic Analyzer with subsequent software analysis using ABI GeneScan 3.1 analysis software (Applied Biosystems). Samples were tested in duplicate.

Results

Grossly, the kidney showed a well defined, whitish mass (5 cm of maximum diameter) involving the renal sinus (Fig. 1), which encircled the ureter narrowing its lumen. The lesion appeared soft and elastic. In the right wall of the bladder, an ulcerated, firm, grayish lesion, infiltrating all the layers was observed. Microscopically, the lesion within the renal sinus consisted of a proliferation of small to medium size lymphocytes (Fig. 2a) sometimes arranged in hyperplastic follicular structures with germinal centers (Fig. 2b). Interfollicular areas were expanded and filled by a diffuse infiltrate of lymphocytes and plasma cells (Fig. 2c); scattered immunoblasts were also identified. The renal parenchyma distant from this lesion was normal and lymphoid infiltration was not detected. Inflammatory

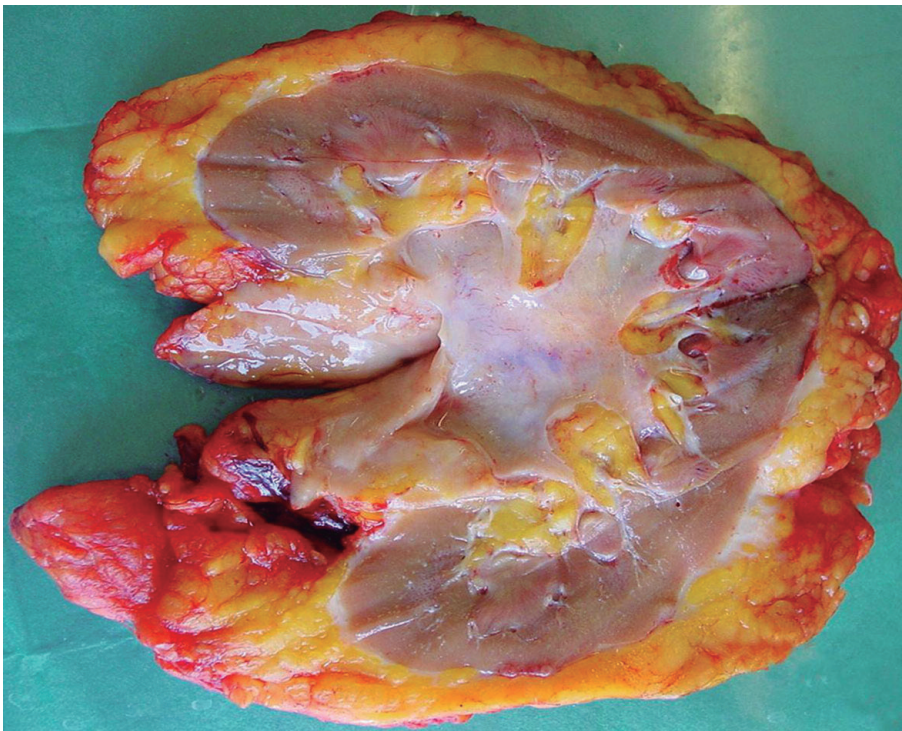


Fig. 1. Macroscopic appearance of left kidney presenting a 5 cm well-defined, whitish, soft and elastic mass involving the renal sinus.

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cells were scattered throughout a hyalinized fibrous tissue, encircling the ureter (Fig. 2d). Mitotic figures, cell pleomorphism and nuclear atypia were absent. Immunohistochemical studies revealed that germinal centers were populated by CD20 positive (Fig. 3a) and Bcl-2 negative (Fig. 3b) lymphocytes. Lymphocytes surrounding the follicular structures and interfollicular areas were positive for CD3 (Fig. 3c) and Bcl-2. CD79a positive cells were scattered in the lymphoid follicles. Plasma cells were positive for CD138 (Fig. 3d) as well as for both kappa and lambda light chains. Ki-67 labeling was about 5%. On the basis of the morphological and immunohistochemical features the diagnosis of PL was made. This diagnosis was confirmed by molecular studies. In fact, the results of B-cell receptor gene rearrangement analysis showed oligo/polyclonal rearrangement with multiple clones

detected in IGH-A, IGH-B and IGH-C tubes, with amplicons falling within the expected size ranges (Fig. 3d, inset bottom right). The bladder lesion was diagnosed as a high grade flat urothelial carcinoma infiltrating all the layers of the wall and the fat tissue (pT3bNxMx, according to TNM7). An acinar adenocarcinoma, Gleason score 6 (pT2aN0Mx, according to TNM7) was also detected in the prostate.

Discussion

Pseudolymphoma is recognized as a well-demarcated, benign tumor lesion, characterized by hyperplastic lymphoid follicles with reactive germinal centers, which consists of polymorphic and polyclonal lymphoid cells, mainly mature lymphocytes and plasma cells, and of inflammatory cells. In the kidney and upper

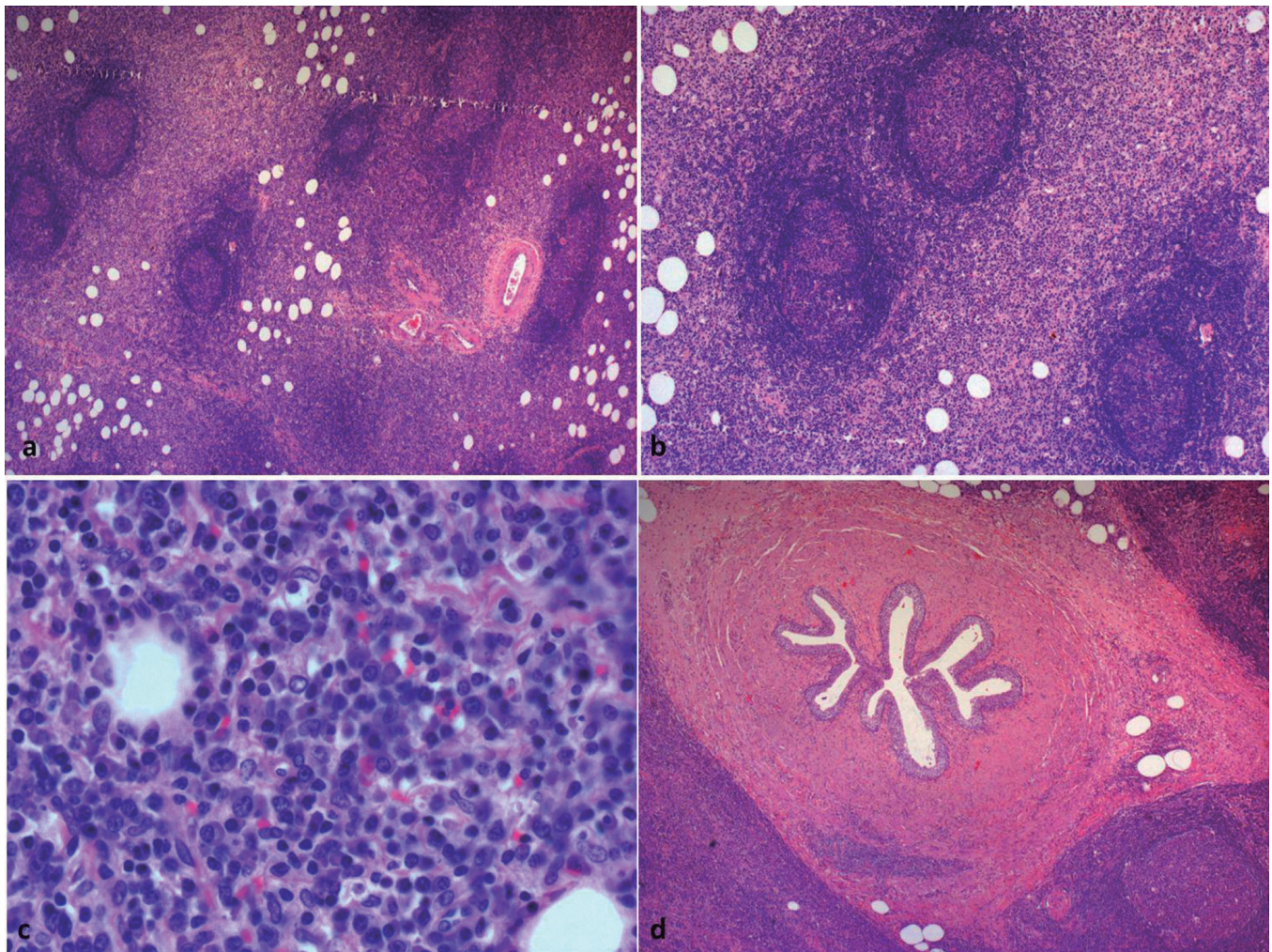


Fig. 2. Microscopic appearance of the PL: proliferation of small to medium size lymphocytes (a) sometimes arranged in hyperplastic follicular structures with germinal centers (b). Interfollicular areas are expanded and filled by a diffuse infiltrate of lymphocytes and plasma cells; scattered immunoblasts are also identified (c). The lesion encircles the ureter (d) (H&E). a, d, x 2.5; b, x 5; c, x 40

urothelial tract it is uncommon (Yuhara et al., 1992; Wada et al., 1993; Fukuda et al., 1995; Cacoub et al., 1996; Kitsukawa et al., 1997; Teranishi et al., 2003). In total, 7 cases have been described, including the case here illustrated, 3 in the renal parenchyma (Fukuda et al.,

1995; Cacoub et al., 1996; Wada et al., 1993), 2 in the perirenal space (Kitsukawa et al., 1997), 1 in the upper ureter (Yuhara et al., 1992) and 1 in the renal pelvis (Teranishi et al., 2003). All lesions were single. The median age of the patients was 62 years (range: 51-70),

Table 1. Clinicopathological features of renal and upper urothelial tract pseudolymphoma described in the literature so far.

Case no.	Author	Sex	Age	Location	Size (cm)	Treatment	Associated disorders
1	Fukude	M	70	Renal parenchyma	2	Surgery	n.a.
2	Wada	F	68	Renal parenchyma	n.a.	Drugs (prednisolone)	Pseudolymphoma of the orbit
3	Cacoub	M	56	Renal parenchyma	4	Drugs (prednisolone)	Sjogren syndrome
4	Yuhara	F	67	Upper urether	0.5	Drugs (prednisolone)	Sjogren syndrome
5	Kitsukawa	F	51	Perirenal space	n.a.	Surgery	n.a.
6	Teranishi	F	52	Renal pelvis	1.5	Drugs (prednisolone)	Sjogren syndrome
7	Ambrosio	M	70	Renal sinus	5	Surgery	High grade urothelial carcinoma of the bladder and prostate adenocarcinoma

n.a.: not available

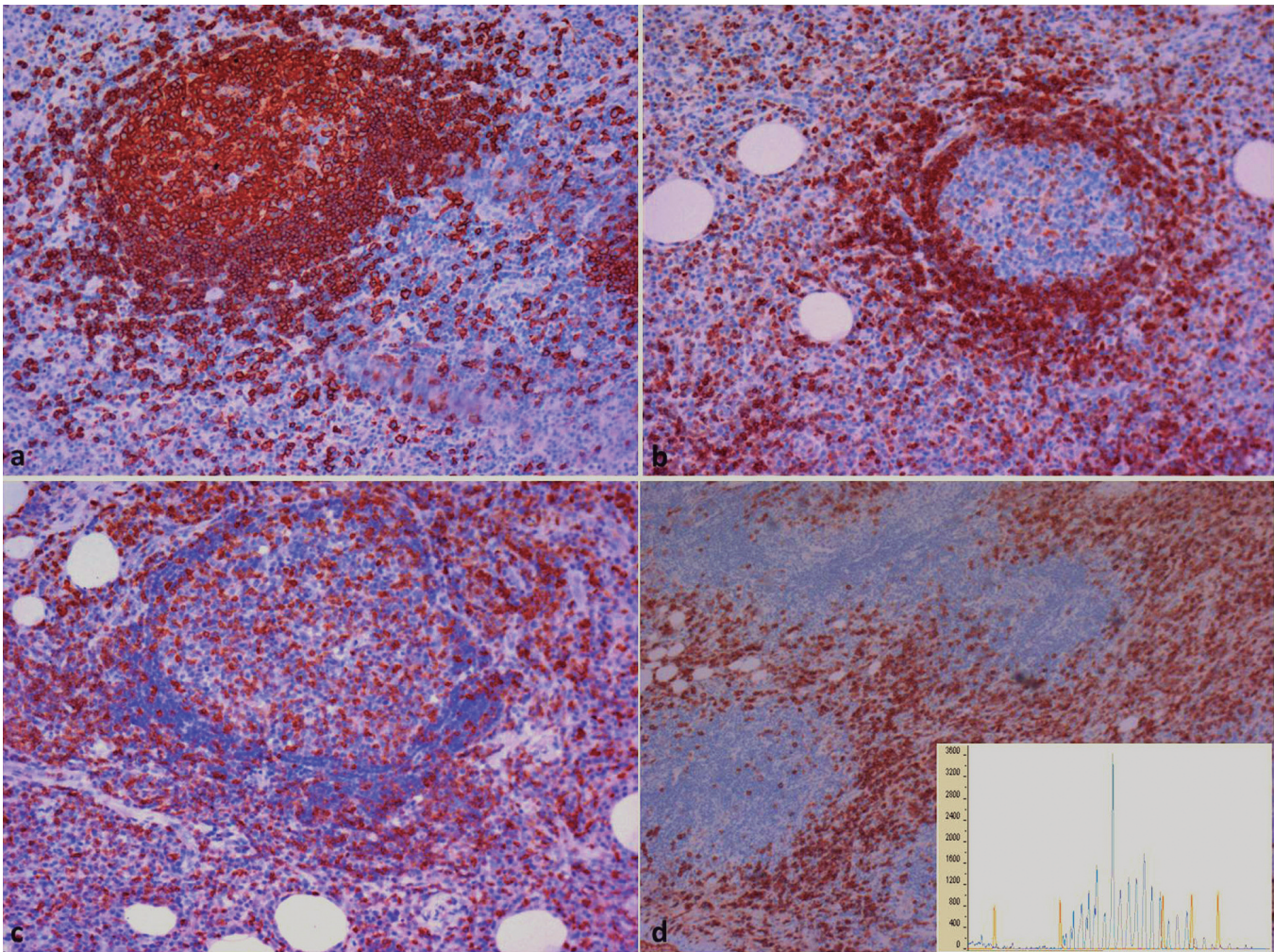


Fig. 3. Germinal centers are composed of CD20 positive (a), Bcl-2 (b) negative lymphocytes. Lymphocytes surrounding the germinal centers and interfollicular areas are positive for CD3 (c). Plasma cells are positive for CD138 (d). GeneScan analysis of multiplex polymerase chain reaction (PCR)-based evaluation of clonal IgH rearrangements shows an irregular Gaussian distribution with multiple clones detected. (d, inset bottom right). x 10

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with a female predominance (57%). The average diameter of the lesions was 2.6 cm (not all data available). Three patients (32.8%) were affected by Sjogren syndrome in extrarenal organs. Only the patient herein described presented malignancies. Clinicopathological and therapy data of all these 7 cases are listed in table 1. The differential diagnosis of PL includes lymphoma and inflammatory pseudotumor (IPT). It is difficult to differentiate pseudolymphoma from lymphoproliferative disorders only on the basis of clinical and radiological data. Therefore, a correct diagnosis can be achieved by means of a meticulous pathological analysis of the lesion with a strict correlation between morphology, immunohistochemistry and molecular biology. The absence of clinicopathological features of IPT (fever, myofibroblastic proliferation, xanthogranulomatous change, phlebitis) and of atypia and mitotic figures of lymphoid cells, together with their oligoclonal rearrangement, as in our case, are in favor of a benign behavior. As mentioned before, the etiology of PL may involve infections, allergic responses, autoimmune reactions and tumors. The relatively high prevalence of Sjogren syndrome, as well as the notion that PL regresses after corticosteroid therapy (Boer et al., 2008; Cacoub et al., 1996; Yuhara et al., 1992) suggest a possible involvement of autoimmunity, but in our case no systemic immunologic abnormalities have been detected. Regarding the association with malignancies, some cases of simultaneous tumors have been described (Sato et al., 2006; Takahashi et al., 2006) and it seems that immunoreaction against neoplastic cells may be associated with the development of PL (Sato et al., 2006). It is also known that, although most PL undergo spontaneous regression, their malignant transformation into true lymphomas has been reported in various organs, such as lung, stomach and skin (Brooks and Enterline, 1983; Koss et al., 1983; Kulow et al., 2002; Nihal et al., 2003). It is unclear whether these cases were firstly misdiagnosed histologically as PL or whether the initial harboring of clones of lymphocytes in the PL was an early step in a multistep progression pathway to lymphoma, supported by persistent antigenic stimulation (Bergman, 2010). The molecular analysis of these cases have showed that are cases with polyclonal rearrangement who less rarely present this evolution. For this reason, although clonal B-cell or T-cell populations may be encountered in clearly benign conditions (Boudova et al., 2005; Bergman et al., 2006), we believe that in idiopathic cases with frankly clonal or also with oligo/polyclonal lymphoid cells, an accurate follow-up should be done.

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