CASE REPORT

Rosai-Dorfman disease of the testis: an unusual entity that mimics testicular malignancy

S M Fernandopulle, J S G Hwang, C H Kuick, J Lui, P H Tan, W-Y Siow, M Wong

J Clin Pathol 2006;59:325–327. doi: 10.1136/jcp.2005.028423

A 47 year old Chinese man with diabetes mellitus and previously treated pulmonary tuberculosis presented with painless right testicular enlargement of 1 month's duration. He underwent an orchidectomy for presumed testicular neoplasm corroborated clinicoradiologically. Histological examination of the testicular mass revealed an inflammatory lesion comprising lymphocytes, plasma cells and sheets of pale staining histiocytes, some containing lymphocytes within their ample cytoplasm, suggestive of emperipolesis. S100 immunohistochemistry stained the histiocytes, while ultrastructural examination confirmed emperipolesis. A diagnosis of Rosai-Dorfman disease was made, an exceedingly rare testicular lesion. Clinicoradiological findings mimicked a neoplasm, while the inflammatory histological appearances with occasionally discerned multinucleated cells raised the possibility of xanthogranulomatous orchitis. Tuberculous orchitis was excluded through negative Ziehl-Neelsen stains and PCR for mycobacterium, while seminoma, which sometimes features a predominant inflammatory component obscuring neoplastic cells, was excluded by absent immunostaining for placental alkaline phosphatase and CD117.

A 47 year old Chinese man presented with a 1 month history of right testicular swelling not associated with fever, pain, or urinary symptoms. He was diabetic, with clinical evidence of nephropathy, and had been previously treated for pulmonary tuberculosis. Clinical examination revealed an enlarged non-tender testicular mass. No inguinal or other lymphadenopathy was palpated. Laboratory investigations yielded a normal full blood count. Serum β HCG was within normal limits; α -fetoprotein level was at the upper limit of normal (10 μ g/L; normal range 1–10). Additional blood investigations were not performed. Chest radiograph disclosed a cavitating lesion in the right upper zone measuring 20×19 mm, with an adjacent soft opacity, radiologically suspicious of tuberculosis. Ultrasound examination of the right testis revealed a well defined 20×30 mm nodule with increased vascularity suggestive of malignancy (fig 1). The patient underwent a right orchidectomy after review of chest radiograph findings concluded inactive tuberculosis.

PATHOLOGICAL FINDINGS

The right orchidectomy specimen weighed 22 g, comprising a 50×28×20 mm testis with attached 35×11 mm spermatic cord. The testis was smooth surfaced with a tan, mostly homogeneous cut appearance. An area 23 mm in dimension was yellowish brown in colour with a softer consistency (fig 2). No other discrete nodules were observed macroscopically.

Light microscopy revealed partially preserved testicular architecture with patchy chronic inflammatory cell infiltrates

Figure 1 Ultrasonographic examination of the right testis showed a mass suggestive of a neoplasm.

Figure 2 Macroscopic appearance of the resected testis, revealing a homogeneous tan cut surface, and a yellowish brown softer area through which an incision has been made for histological sampling.

comprising lymphocytes, plasma cells, and aggregates of histiocytes. Sections from the softer yellowish brown area demonstrated more prominent inflammatory cells, with histiocytes occurring in sheets (fig 3A). Some histiocytes were intimately associated with lymphocytes that appeared to reside within their pale, almost xanthomatous cytoplasm, suggesting emperipolesis (fig 3B). Rare multinucleated giant cells and epithelioid histiocytes were found (fig 3C), but caseating granulomas were not seen. Ziehl-Neelsen and fungal (periodic acid-Schiff, Gomori-methenamine silver) stains were negative. No abnormal “seminoma-like” cells with enlarged vesicular nuclei and distinct nucleoli were discovered among the inflammatory cells.

Residual testicular tissue featured sclerosed and hyalinised seminiferous tubules in a fibrotic background with few small diminutive tubules at the periphery lined by Sertoli cells. No

Abbreviations: RDD, Rosai-Dorfman disease; XO, xanthogranulomatous orchitis

Figure 3 (A) Sheets of pale histiocytes admixed with lymphocytes and plasma cells. (B) An intimate association of histiocytes with lymphocytes and plasma cells, some appearing to reside within histiocytic cytoplasm, suggesting emperipolesis. (C) An aggregate of epithelioid histiocytes found among the inflammatory infiltrates; no caseation was seen.

intratubular germ cell neoplasia or active spermatogenesis was seen. Groups of Leydig cells were present between hyalinised tubules. Dystrophic calcification was present focally.

Immunohistochemistry for CD68 and S100 showed positive staining histiocytes, accentuating engulfed lymphocytes and plasma cells, confirming emperipolesis (fig 4). Placental alkaline phosphatase (PLAP) and CD117 immunostains were negative. There was no staining of histiocyte-like cells by CD1a. Table 1 shows details of the antibodies.

Figure 4 Immunohistochemistry for S100 decorates histiocytes with engulfed lymphocytes.

As the testis had been extensively sampled for histological evaluation, with representative lesional areas mostly processed by paraffin wax embeddding, electron microscopy was carried out on reprocessed material derived from the paraffin block, using previously described methods.¹ Ultrastructural study showed histiocytes, lymphocytes, and plasma cells, with rare histiocytes containing lymphocytes within their cytoplasm, in keeping with emperipolesis (fig 5).

Although the Ziehl-Neelsen stain was negative, it was deemed necessary to exclude, using more sensitive molecular techniques, the possibility of underlying tuberculous infection in the light of a previous history, chest radiography findings, and the occasional, although rare, occurrence of multinucleated cells and epithelioid histiocytes within the testicular lesion. DNA was extracted from paraffin sections and subjected to PCR for *Mycobacterium tuberculosis* using appropriate primers and controls. A positive result would give

Figure 5 Emperipolesis was confirmed ultrastructurally with two lymphocytes revealing clumped chromatin within the cytoplasm of a histiocyte containing a more ovoid nucleus with open chromatin.

Table 1 Details of antibodies, dilutions and antigen retrieval methods				
Antibody	Catalogue No.	Clone	Dilution	Pretreatment method
CD68	Dako M0814	KP1	1:300	10 min 0.1% α -chymotrypsin pH7.8 at 37°C
CD117	Dako A4502	Rabbit polyclonal 8A9	1:200	Pressure cook in MW (using Milestone T/T Mega) in Dako S3307 Hi-pH at 110°C for 2 min and after rapid cooling, incubate for 10 min
PLAP	Dako M7191		1:100	25 min MW (using National MW oven NN-S650 WF) at 50% setting in Dako S1699 buffer pH 6. After rapid cooling, incubate for 10 min
CD1a	Ventana 250-2729	JPM30	Predilute	Pressure cook in MW (using Milestone T/T Mega) at 115°C for 2 min in 0.01 mol/l citrate buffer pH 6, and after rapid cooling, incubate for 10 min
S100	Dako Z0311	Rabbit polyclonal	1:1000	Nil

MW, microwave.

a 123 bp product band. The index case did not disclose any product band, therefore confirming a negative result. The final pathological diagnosis was Rosai-Dorfman disease (RDD) of the right testis.

Postoperative recovery was uneventful and the patient was well at last follow up, 4 months after orchidectomy.

DISCUSSION

RDD is an idiopathic histiocytic proliferative disorder originally described by Rosai and Dorfman in 1969.² The clinical features include massive painless lymphadenopathy, fever, and polyclonal hypergammaglobulinaemia. Most cases occur during the first or second decades of life, but any age group can be affected. With widespread geographic distribution and predisposition for black populations, extranodal involvement is reported in up to 25% of cases, with practically all organ systems affected, most commonly the eyes and ocular adnexa, head and neck region, upper respiratory tract, skin and subcutaneous tissue, and central nervous system.²⁻³ Other sites include the gastrointestinal tract, salivary glands, genitourinary tract, thyroid, and breast.³⁻⁵ Despite the apparent description of genitourinary disease, there has been to date only one report of testicular RDD, in a patient who developed the condition 12 years after the diagnosis of lymphoma.⁶ Another account in 1966 discussed a histiocytic proliferative disease manifesting as testicular enlargement, severe lymphadenopathy, transient hepatomegaly, hypergammaglobulinaemia, recurrent infections, and rheumatoid arthritis in a boy, and, although emperipolesis was not documented in the pathological specimens of the testis or lymph node, it is plausible that this case in fact represented RDD prior to its initial formal description,⁷ and thus the earliest example of testicular RDD.

The spleen and bone marrow are usually spared in RDD. For cases that are primarily nodal in presentation, about 43% also demonstrate at least one site of extranodal disease.³ The pathological features of RDD have been well described, and characteristic S100 positive histiocytes with emperipolesis remain the microscopic hallmark.²⁻⁴ In our patient, testicular RDD resulted in a clinical swelling for which a neoplasm was the prime consideration, supported by ultrasonographic examination. Even on microscopy, the presence of an admixture of histiocytes, lymphocytes, and plasma cells, together with occasional multinucleated giant cells, brought forth a differential diagnosis of xanthogranulomatous orchitis (XO), a lesion which has been reported more frequently than testicular RDD.⁸ XO is believed to be aetiologically related to immunological defects, chronic infection and abnormal phagocytosis. In fact, because of the difficulty of detecting emperipolesis in extranodal RDD^{3-4,9} as in our case, it is possible that a diagnosis of XO would have been rendered if a thorough search for emperipolesis or confirmation of S100 positive histiocytes had not been performed. The presence of rare multinucleated cells and several epithelioid histiocytes in our case is unusual for RDD, and may be explained as a response to disrupted seminiferous tubules, as an infective cause had been excluded. Malakoplakia was the other possible histological differential diagnosis, though the absence of Michaelis-Guttman bodies essentially excluded this likelihood.

It was especially critical to exclude a testicular neoplasm, particularly since burnt out seminomas or seminomas with prominent accompanying inflammatory infiltrates may disclose few neoplastic cells obscured by inflammation.¹⁰ This can be readily addressed with immunostaining for PLAP and CD117. The lack of intratubular germ cell neoplasia was also a helpful feature.

The occurrence of RDD in our patient with diabetes and past pulmonary tuberculosis raises questions of whether these conditions are related. Our previous report of RDD of

TAKE HOME MESSAGES

- Rosai-Dorfman disease (RDD) is an idiopathic histiocytic proliferative disorder.
- Extranodal involvement is reported in up to 25% of cases, with practically all organ systems affected, but despite the apparent description of genitourinary disease, there has been to date only one report of testicular RDD.
- In our patient, the microscopic appearance suggested a diagnosis of xanthogranulomatous orchitis, showing the difficulty of diagnosing RDD.

the breast included one patient with diabetes.⁵ Although the pathogenesis of RDD is still not fully elucidated, infective or immune mediated causes are plausible.¹¹ The fact that diabetic patients are more susceptible to infections suggests possible immunological defects that may potentially predispose to RDD. The clinical course of RDD is generally benign, though there are reports of progressive disease.³⁻⁴

In summary, testicular RDD is difficult to diagnose preoperatively, mimicking a testicular neoplasm clinicoradiologically. On microscopy, XO is a histological differential. A high index of suspicion is needed to identify typical histiocytes with emperipolesis. A possible relationship with systemic diseases such as diabetes needs to be explored.

Authors' affiliations

S M Fernandopulle, J S G Hwang, C H Quick, J Lui, P H Tan, Department of Pathology, Singapore General Hospital

W-Y Siow, M Wong, Department of Urology, Singapore General Hospital

Correspondence to: Dr P H Tan, Department of Pathology, Singapore General Hospital, Outram Road, Singapore 169608; gptph@sgh.com.sg

Accepted for publication 19 April 2005

REFERENCES

- 1 Tan PH, Lui GG, Chiang G, *et al*. Ductal carcinoma in situ with spindle cells: a potential diagnostic pitfall in the evaluation of breast lesions. *Histopathology* 2004;**45**:343-51.
- 2 Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a newly recognized benign clinicopathologic entity. *Arch Pathol* 1969;**87**:63-70.
- 3 Foucar E, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. *Semin Diagn Pathol* 1990;**7**:19-73.
- 4 Juan Rosai. Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy). In: *Rosai and Ackerman's surgical pathology*, 9th ed. Mosby, Philadelphia, 2004:1911-13.
- 5 Ng SB, Tan LHC, Tan PH. Rosai-Dorfman disease of the breast: a mimic of breast malignancy. *Pathology* 2000;**32**:10-15.
- 6 Lossos I S, Olkon E, Bogomolski-Yahalom V, *et al*. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): report of a patient with isolated renotesticular involvement 12 years after cure of non-Hodgkin's lymphoma. *Ann Hematol* 1997;**74**:41-4.
- 7 Azoury FJ, Reed RJ. Histiocytosis. Report of an unusual case. *N Engl J Med* 1966;**274**:928-30.
- 8 Nistal M, Gonzalez-Peramato P, Serrano A, *et al*. Xanthogranulomatous funiculitis and orchiepididymitis. Report of 2 cases with immunohistochemical study and literature review. *Arch Pathol Lab Med* 2004;**128**:911-14.
- 9 Warnke RA, Weiss LM, Chan JKC, *et al*. Histiocytic and dendritic cell proliferations. In: *Atlas of tumor pathology. Tumors of the lymph nodes and spleen*. Washington DC: American Registry of Pathology, 1995:349-60.
- 10 Woodward PJ, Mostofi FK, Tolleran A, *et al*. Germ cell tumours. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *World Health Organization classification of tumours. Pathology and genetics. Tumours of the urinary system and male genital organs*. Lyon: IARC Press, 2004:230-3.
- 11 Miettinen M, Pajakka P, Haveri P, *et al*. Sinus histiocytosis with massive lymphadenopathy. A nodal and extranodal proliferation of S-100 protein positive histiocytes? *Am J Clin Pathol* 1987;**88**:270-7.