case report

Wien Klin Wochenschr (2016) 128:442–446
DOI 10.1007/s00508-015-0807-6

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Detection of Epstein–Barr virus in inflammatory pseudotumour of the spleen: a case report

Marko Mance · Ivan Romić · Matea Majerović

Received: 17 February 2015 / Accepted: 11 May 2015 / Published online: 25 June 2015

Summary
Background Various types of benign and malignant splenic tumours including hemangiomas, lymphagiomas, hamartomas, hemangiosarcomas, malignant lymphomas and metastatic carcinomas share radiological characteristics making it impossible for a physician to determine the definite aetiology of splenic masses noninvasively without histopathological evaluation. It is important that physicians recognize the importance of a careful and continuous follow-up since inflammatory pseudotumours (IPT) are considered to be tumours with an intermediate malignant potential based on their behaviour when they arise in other locations.

Methods Our patient, a 60-year-old woman was evaluated using laboratory, gastroscopy, computed tomography and surgical methods. The resected tumour was evaluated using immunohistochemical methods.

Results The patient presented with weight loss, nausea and vomiting, symptoms lasting over a course of a few months. The splenic mass was found incidentally at the time of work up for gastritis and cholelithiasis. Histologically, the tumour differed from typical splenic architecture being composed of atypical spindle cells with inflammatory elements; numerous plasma cells, macrophages, eosinophils and lymphocytes.

Conclusions Although very difficult to diagnose at initial presentation, it is very important for the physician to be aware of the importance of a careful diagnosis since IPT of the spleen are rare and considered to be tumours with an intermediate malignant potential

Keywords Computed tomography · Epstein–Barr virus · Eosinophil follicular dendritic cell tumour · Hematoxylin and eosin stain · Splenic inflammatory pseudotumour

Dr. M. Mance (✉) · I. Romić, MD
Department of Surgery, University of Zagreb,
Zagreb University Hospital Center,
Kišpatićeva 12,
10000 Zagreb, Croatia
e-mail: markomance@gmail.com

M. Majerović, MD
Department of Internal Medicine, University of Zagreb,
Zagreb University Hospital Center,
Zagreb, Croatia

Introduction

Inflammatory pseudotumours (IPT) are an uncommon type of tumour composed of proliferative spindle cells of unknown origin which mimic other tumours at clinical and histological evaluation [1]. IPT usually presents as a well-circumscribed, mostly solitary mass containing foci of inflammatory plasma and lymphocyte cells in a fibroblastic stroma [2].

Various types of benign and malignant splenic tumours including hemangiomas, lymphagiomas, hamartomas, hemangiosarcomas, malignant lymphomas and metastatic carcinomas share radiological characteristics making it impossible for a physician to determine the definite aetiology of splenic masses noninvasively without histopathological evaluation.

IPT are known to occur in areas other than the spleen including the orbit, respiratory tract, gastrointestinal tract, liver and others; however, splenic IPT are extremely rare occurences. Therefore, when we detect a splenic mass radiologically, a lymphoma is most often clinically suspected. A true diagnosis of IPT is usually revealed only after the spleen is removed and examined histologically [3, 4].

When compared to IPT's that occur at other anatomic locations, splenic tumours typically have the presence of the Epstein–Barr virus (EBV), suggesting a distinctly different pathogenetic pathway in these locations [5–10]. The incidence of benign splenic tumours is 0.007 %

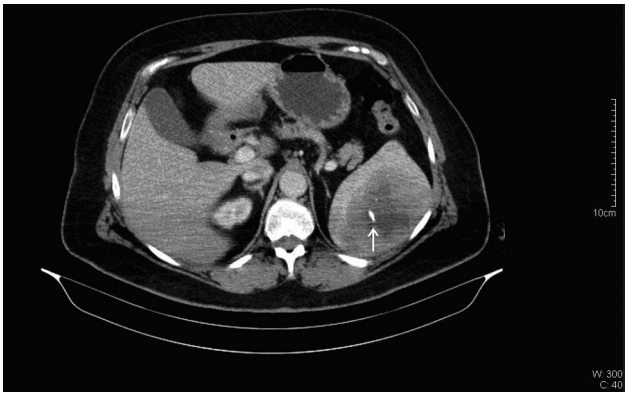

Fig. 1 Computed tomography scan of the abdomen demonstrates an 8 cm solitary solid appearing splenic mass with a central necrotic lesion (*arrow*)

among all subjects on whom an operation or autopsy is performed and to our knowledge, there have been only approximately 130 documented cases of IPT since it was first mentioned in medical literature in 1984 [11].

In this paper, we describe a case of EBV positive inflammatory pseudotumour of the spleen.

Materials and methods

A 60-year-old woman was admitted to our hospital complaining of weight loss, nausea and vomiting, with symptoms persisting over a period of a couple of months. Prior diseases included epilepsy and chronic migraines while her family history lacked any similar illnesses or symptoms. The physical examination did not reveal any signs of abdominal tenderness, lymphadenopathy or organomegaly while most of the laboratory findings registered in the normal ranges, except for C-reactive protein (CRP) (12,1 ↑ (normal range: 0–5)) and alkaline phosphatase (ALP) (63 ↓ (normal range: 64–153)).

The patient was evaluated due to gastroenterologic symptoms. During the diagnostic workup, a well-defined, solid mass measuring 8.0 cm in diameter with a central necrotic lesion was discovered on multislice computed tomography (MSCT) examination (Fig. 1).

The most common primary sources of splenic metastasis are breast, lung, colorectal and ovarian carcinomas and melanoma in cases of multivisceral cancer and colorectal and ovarian carcinomas in cases of solitary splenic lesion. It was first suspected that the lesion was due to a metastasis but esophagogastroduodenoscopy and other examinations failed to determine a primary cause. The patient was diagnosed with gastritis and duodenitis which accounts for the associated symptoms of nausea and vomiting which were most likely due to the inflammation of the gastric and intestinal mucosa and not the inflammatory pseudotumour.

We suspected that the mass was either a hematoma, hemangioma, inflammatory pseudotumour or malignant lymphoma and it was decided that a splenectomy

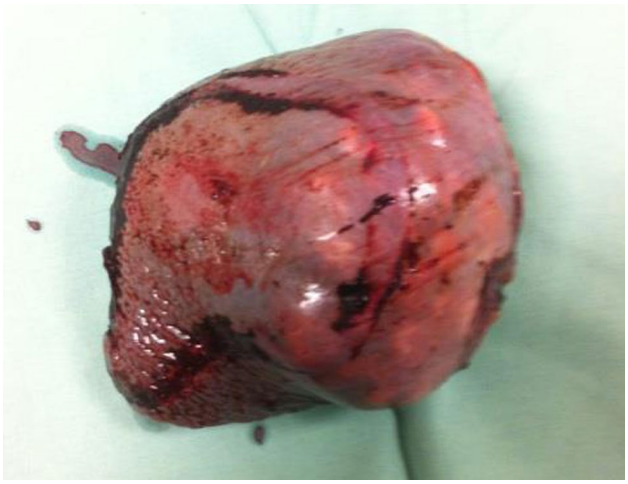

Fig. 2 The resected spleen before dissection

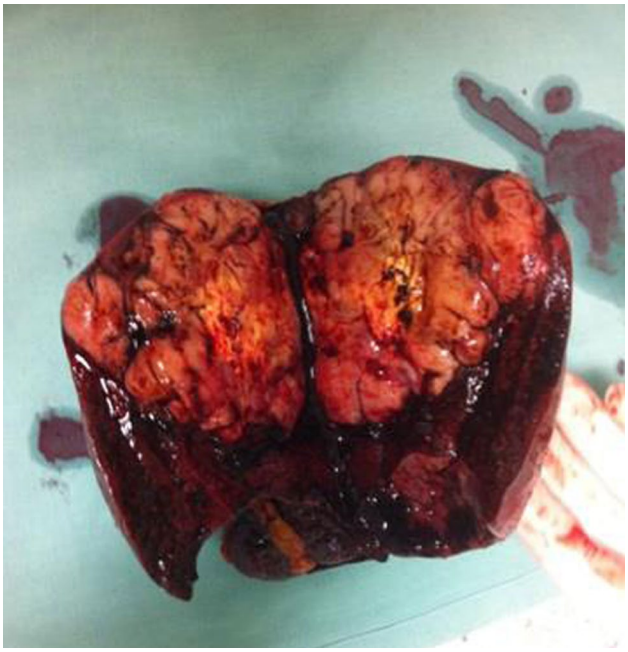

Fig. 3 The dissected spleen with the visible tumorous mass. The dissected surface of the mass is lobulated, well circumscribed, *tan-yellow*, and bulging

by a classic laparotomy is the best method of management. The operation was performed 7 days after admission. Intraoperativly, there were no indications of local tumour invasion, with the liver, kidneys and local lymph nodes visually unremarkable. The postoperative course proceeded without any complications. The patient is currently alive and asymptomatic, 2 months after surgery.

The spleen measured 14 cm × 13 cm × 7 cm. The tumour was a yellowish-tan, well-circumscribed, lobulated mass measuring 8.4 cm in diameter. (Fig. 2, 3, 4).

Histologically, the tumour differed from typical splenic architecture being composed of atypical spindle cells with inflammatory elements: numerous plasma cells, macrophages, eosinophils and lymphocytes with

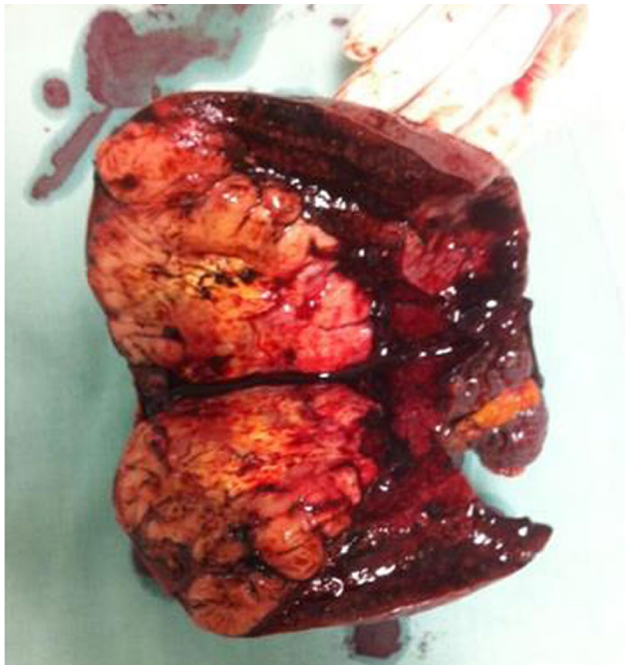

Fig. 4 The dissected spleen with the visible tumorous mass. The dissected surface of the mass is lobulated, well circumscribed, *tan-yellow*, and bulging

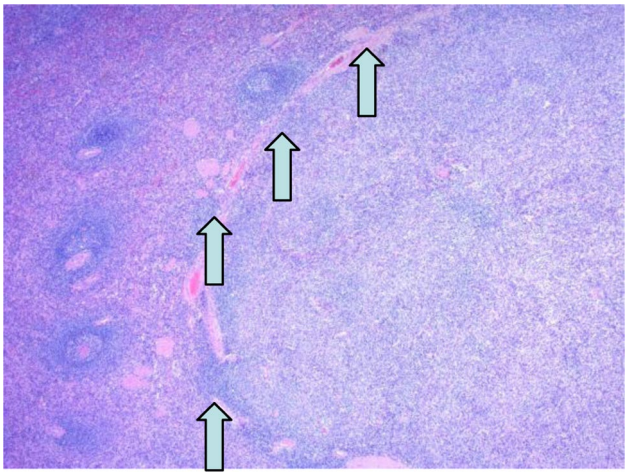

Fig. 5 Hematoxylin and eosin staining 2.5× magnification. Histologic section of splenic mass shows a normal splenic architecture on the *left* with the well demarcated atypical achitecture to the *right*. (*Arrows* show the border between normal and abnormal architecture)

atypical cell morphology. (Fig. 5, 6). The surrounding tissue was composed of normal cell architecture.

There were also areas of hyalinised connective tissue infiltration. An immunohistochemical analysis was performed and revealed EBV encoded small nuclear RNA (EBER) and CD68 positive markers (Fig. 7). CD20, CD3, CD31, CD21, CD23 and ALK1 were all found to be negative.

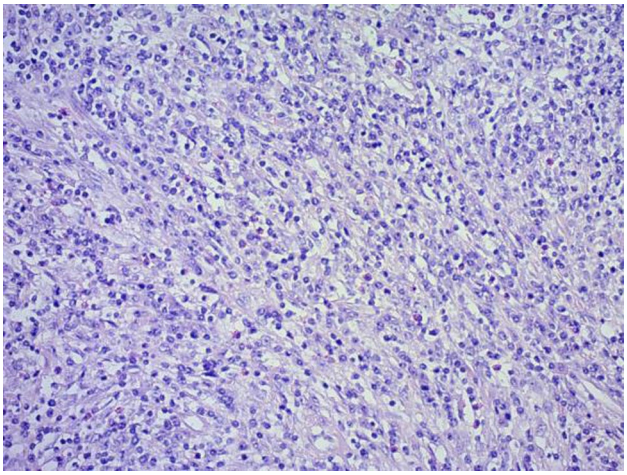

Fig. 6 Hematoxylin and eosin staining 20× magnification. Histologic section of splenic mass shows multiple cell types including T and B lymphocytes, plasma cells and eosinophils

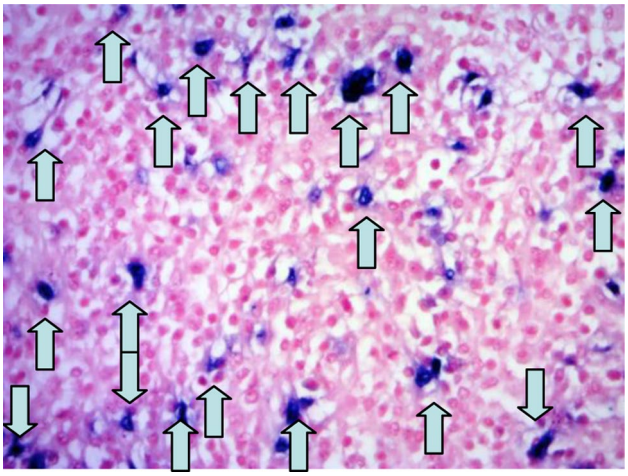

Fig. 7 In situ hybridization using Epstein–Barr virus (EBV)-encoded small RNA probes demonstrates EBV-positive cells in scattered oval to spindle cells. (indicated by *arrows*)

Results

We compared our histological and immunohistochemical results to similar cases of IPT of the spleen with the presence of EBV previously described in literature and had similar findings. Our patient had a tumour that differs from typical splenic architecture (atypical spindle cells), EBV was detected within the tumour but not in the surrounding tissues and an increased number of EBV encoded small nuclear RNA was found. Therefore, a final diagnosis of inflammatory pseudotumour of the spleen with the presence of EBV was made.

Discussion

Inflammatory pseudotumour of the spleen is an very rare benign lesion found in approximately 0.007 % of all

subjects on whom an operation or autopsy is performed. It presents as a well-circumscribed mass which is usually solitary and composed of foci of inflammatory cells, mainly plasma cells and lymphocytes within a fibroblastic stroma [2, 11].

These tumours are known to occur more frequently in areas other than the spleen including the orbit, respiratory tract, gastrointestinal tract, liver and others. Due to the rarity of this tumour type, when primary splenic tumours are diagnosed, a lymphoma is most often clinically suspected and although modern imaging examinations have greatly improved, a true diagnosis of IPT is most frequently revealed only after the resected spleen histologically being examined [3, 4].

IPT of the spleen have been known to undergo non-aggressive clinical courses without local recurrences or metastases if the lesions are removed completely. As described by Coffin et al. [12], these lesions are most often benign, non-metastasising proliferations of myofibroblasts. The prognosis of IPT's is favourable following splenectomy as there have been no reported cases of patients with metastatic disease. However, there have been cases of certain patients with IPTs of the liver, who have died as a result of disease progression [13]. Meis and Enzinger [14] documented the locally aggressive and recurrent nature of these specific neoplasms and suggest that they can potentially be malignant. The World Health Organization classification of soft tissue tumours places IPT in an intermediate category (Rarely metastasising, <5%), between benign and malignant [15].

As mentioned above, IPT are most frequently diagnosed after histological examination because of the various types of splenic tumours that present in a similar radiologic manner. The follicular dendritic cell tumour (FDC) described by Lewis et al. is an example of an atypical splenic tumour that poses a diagnostic dilemma for the physican. When compared to IPT's, it presents with a similar microscopic appearance. It is composed of minimal to moderate atypia of the spindle cells and is positive for CD21, CD23 and CD35 markers [10]. This is potentially a good method of distinction since in our case, CD 21 and CD 23 were found to be negative.

Inflammatory myofibroblastic tumours (IMT), which are anaplastic lymphoma kinase (ALK) positive and EBV negative have frequently been described as synonyms of IPTs. This relationship has been described by various authors [12, 14–17] although more recent publications by Kutok et al., Neuhauser et al. and the Stanford Surgical Pathology Criteria have described the two as distinct entities based on the absence of ALK in IPT's, making them biologically distinct from the histologically similar IMT [16, 18, 19].

When an IPT is suspected, mycobacterial spindle cell pseudotumours should also be included as a potential differential diagnosis in patients who are immunocompromised such as human immunodeficiency virus (HIV) infected individuals, cardiac transplant patients, patients with diabetes and patients treated with immunosuppressive medications. It is described as being composed of CD68 positive proliferating spindle cells which contain mycobacterium. It is important for the physician to recognise that this lesion is infective and that the management therefore differs from other splenic tumours which are neoplastic in nature [20, 21].

In this study, we report the presence of EBV in an IPT involving the spleen in a 60-year-old woman who was admitted to our hospital complaining of weight loss, nausea and vomiting lasting a couple of months. Incidentally, during the diagnostic workup, an enlarged spleen with a well-defined, solid mass measuring 8.0 cm in diameter with a central necrotic lesion was discovered on MSCT examination.

Histologically, the tumour differed from typical splenic architecture being composed of atypical spindle cells with inflammatory elements; numerous plasma cells, macrophages, eosinophils and lymphocytes. There were also areas of hyalinised connective tissue infiltration. An immunohistochemical analysis was performed and revealed EBV encoded small nuclear RNA (EBER) and CD68 positive markers, while CD20, CD3, CD31, CD21, CD23 and ALK1 were all found to be negative. A final diagnosis of EBV-associated inflammatory pseudotumour of the spleen was made.

Additional studies with more cases are needed to further define the nature of these rare EBV proliferations within the spleen.

Conclusion

IPT of the spleen is a rare tumour that is not associated with any specific clinical or radiological finding and therefore is most often misdiagnosed as a splenic neoplasm of different origin or composition. There currently lacks an adequate preoperative diagnostic method that could distinguish between the various types of splenic tumours and most IPT are detected incidentally following histopathological and immunohistochemical analysis of the resected spleen. IPT's of the spleen are regarded as benign lesions since tumour recurrence and metastasis has not been documented. Regardless, it is very important for the physician as well as the patient to recognize the importance of a careful and continuous follow-up since IPTs are considered to be tumours with an intermediate malignant potential based on their behaviour when they arise in other locations.

Disclosure

I certify that all my affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g. employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties).

Compliance with ethical guidelines

All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. For studies with human subjects include the following: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 [5].

Conflict of interest

Marko Mance, Ivan Romić, and Matea Majerović declare that there is no conflict of interest.

References

1. Rajabi P, Noorollahi H, Hani M, Bagheri M. Inflammatory pseudotumor of spleen. Adv Biomed Res. 2014;3:29.
2. Kalaivani V, Vijayakumar HM, Girish KS, Hegde N. Inflammatory pseudotumour of the spleen: a diagnostic dilemma. Clin Diagn Res. 2013;7(7):1460–2.
3. Jiqi Y, Chenghong P, Weiping Y, Chenghua W, Jiazeng D, Ting S, Hongwei L. Inflammatory pseudotumour of the spleen: report of 2 cases and literature review. Can J Surg. 2008;51(1):75–6.
4. Loughlin P, Brady A, Devlin E, McManus DT, Spence RA. Epstein-Barr virus positive inflammatory pseudo-tumour of the spleen: a case report and literature review. Int J Surg Case Rep. 2014;5(4):186–8
5. Horiguchi H, Matsui-Horiguchi M, Sakta H, Ichinose M, Yamamoto T, Fujiwara M, Ohse H. Inflammatory pseudotumor-like follicular dendritic cell tumor of the spleen. Pathol Inter. 2004;54:124–31. doi:10.1111/j.1440–1827.2004.01589.x.
6. Oz Puyan F, Bilgi S, Unlu E, Yalcin O, Altaner S, Demir M, Cakir B. Inflammatory pseudotumor of the spleen with EBV positivity. Report of a case. Eur J Haematol. 2004;72:285–91.
7. Cheuk W, Chan JKC, Shek TWH, et al. Inflammatory pseudotumor-like follicular dendritic cell tumor. A distinctive low-grade malignant intra-abdominal neoplasm with consistent Epstein-Barr virus association. Am J Surg Pathol. 2001;25:721–31.
8. Arber DA, Kamel OW, Rijn M, Davis RE, Medeiros LJ, Jaffe ES, Weiss LM. Frequent presence of the Epstein-Barr virus in inflammatory pseudotumor. Hum Pathol. 1995;26:1093–8. doi:10.1016/0046–8177(95)90271-6.
9. Arber DA, Weiss LM, Chang KL. Detection of Epstein-Barr virus in inflammatory pseudotumor. Semin Diagn Pathol. 1998;15:155–60.
10. Lewis JT, Gaffney RL, Casey MB, Farrell MA, Morice WG, Macon WR. Inflammatory pseudotumor of the spleen associated with a clonal Epstein-Barr virus genome. Case report and review of the literature. Am J Clin Pathol. 2003;120:56–61
11. Natsugoe S, Ohwaki T, Tsubouti H, Mitsuda K, Maenohara S, Takao S, et al. Inflammatory pseudotumor of the spleen: report of a case. Surg Today. 1993;23:246–50.
12. Coffin CM, Watterson J, Priest JR, Dehner L. Extrapulmonaryinflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol. 1995;19:859–72.
13. Horiuchi R, Uchida T, Kojima T, Shikata T. Inflammatory pseudotumor of the liver: clinicopathologic study and review of literature. Cancer. 1990;65:1583–90.
14. Meis JM, Enzinger FM. Inflammatory fibrosarcoma of the mesenteryand retroperitoneum. A tumor closely simulating inflammatorypseudotumor. Am J Surg Pathol. 1991;15:1146–56.
15. Coffin CM, Humphrey PA, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor: a clinical and pathological survey. Semin Diagn Pathol. 1998;15:85–101.
16. Neuhauser TS, Derringer GA, Thompson LDR, et al. Splenic inflammatory myofibroblastic tumor (inflammatory pseudotumor) a clinicopathologic and immunophenotypic study of 12 cases. Arch Pathol Lab Med. 2001;125:379–85.
17. Oshiro H, Nomura M, Yamanaka S, et al. Splenic inflammatory pseudotumor (inflammatory myofibroblastic tumor). J Clin Exp Hematopathol. 2007;47:83–8.
18. Kutok JL, Pinkus GS, Dorfman DM, Fletcher CD. Inflammatory pseudotumor of lymph node and spleen: an entity biologically distinct from inflammatory myofibroblastic tumor. Hum Pathol. 2001;32:1382–87.
19. Kempson RL, Rouse RV. Stanford School of Medicine. Surgical pathology criteria: inflammatory myofibroblastic tumor [Internet]. 2008. http://surgpathcriteria.stanford.edu/softfib/inflammatory_myofibroblastic_tumor/printable.html. Accessed 15 June 2008/15 May 2008.
20. Suster S, Moran CA, Blanco M. Mycobacterial spindle-cell pseudotumor of the spleen. Am J Clin Pathol. 1994;101:539–42.
21. Tan GC1, Yap YP, Shiran MS, Sabariah AR, Pathmanathan R.Cutaneous mycobacterial spindle cell pseudotumour.BMJ Case Rep. 2009;2009. pii: bcr11.2008.1221. doi: 10.1136/bcr.11.2008.1221. Epub 2009 Apr 14.