European Journal of Radiology Open 6 (2019) 97–100

Contents lists available at ScienceDirect

European Journal of Radiology Open

journal homepage: www.elsevier.com/locate/ejro

Secondary aneurysmal bone cyst in Langerhans cell histiocytosis: Case report, literature review

P. Lomoro[a], I. Simonetti[b,*], G. Vinci[c], V. Fichera[d], L. Tarotto[b], P. Trovato[b], M.S. Prevedoni Gorone[e]

[a] Department of Diagnostic Medicine Institute of Radiology, IRCCS San Matteo University Hospital Foundation, Pavia, Italy
[b] Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy
[c] Department of Nephrology, University of Campania "Luigi Vanvitelli", Naples, Italy
[d] Department of Pediatrics, Anna Meyer Children's University Hospital, Florence, Italy
[e] Department of Diagnostic and Interventional Radiology and Neuroradiology of IRCCS San Matteo University Hospital Foundation, Pavia, Italy

ARTICLE INFO

Keywords:
Langerhans cell histiocytosis (LCH)
Aneurysmal bone cysts (ABC)
Pediatric bone tumors
Magnetic resonance imaging (MRI)
Radiograph (X-ray)

ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease of the myeloid precursor cells, it predominantly occurs in the skull and long bones as unifocal bone lesions. Aneurysmal bone cysts (ABC) are benign, expansive and lytic bone. Reports of secondary ABC occurring in LCH are rare, having only been reported twice in the skull. Here, we report the first case of LCH masquerading as ABC in a 14-month-old female child who presented with a rapidly growing mass in her left femur. The lesion had typical radiological features of ABC, and only histological examination revealed the presence of cells suggestive of LCH.

1. Introduction

Langerhans cell histiocytosis (LCH) is a rare disease of the myeloid precursor cells, characterised by uncontrolled proliferation and accumulation of CD1a+/CD207+ dendritic cells [1]. It predominantly occurs in the skull and long bones as unifocal bone lesions, but multifocal single-system or multi-system forms should be excluded.

Aneurysmal bone cysts (ABCs) are benign, expansive, lytic bone lesions that produce cavities within the bone that fill with blood, which are lined by proliferative fibroblasts, giant cells and trabecular bone. The extremities are the common skeletal sites. The two main forms of ABC are primary (or classical) and secondary. The development of secondary ABC in LCH is rare, with only two reported occurrences in the skull in the literature. Here, we report the first case of LCH masquerading as ABC in the femur.

2. Case report

A 14-month-old female child with cystic fibrosis presented with a rapidly growing mass in her left thigh. Two months before, she had undergone antibiotic therapy for cellulitis of both inferior legs. On physical examination, the thigh was hot, but there were no signs of injury or a cutaneous rash. She was apyretic with normal vital signs, and her general condition was good. Routine blood and urine tests were normal.

The X-ray showed a large multiloculated osteolytic intraosseous lesion with a well-defined borders, located on the femur from the proximal to the distal diaphysis, accompanied by swelling and "wine fiasco" bone deformity. Thinning and irregularity of the cortical bone were present (Fig. 1).

An MRI confirmed the presence of large multiloculated cystic lesions with defined but irregular borders, characterised by a low and non-homogeneous signal in T1-weighted images and strong signals in T2-weighted and STIR images, with fluid-fluid levels present in the axial sections. The septa presented a low signal intensity in all sequences. No calcifications were found. Oedema of the spongeous bone tissue and the soft tissue were present, in addition to the periosteal reaction. After administration of a paramagnetic endovenous contrast agent (gadoterate meglumine), only a slight rim of septa enhancement was revealed, with no signs of infiltration of adjacent tissues (Fig. 2). The radiological aspects of the lesions were suggestive of an ABC, and a biopsy was performed. Histological examination showed typical characteristics of an ABC, but proliferation of cells with typical characteristics of Langerhans cells was evident in some specimens, with cells

* Corresponding author at: Department of Advanced Biomedical Sciences, University of Naples Federico II, Via Sergio Pansini, 5, 80131 Napoli, Italy.
E-mail addresses: lmr.pcl89@gmail.com (P. Lomoro), igino.simonetti@gmail.com (I. Simonetti), giorgia.vinci@hotmail.it (G. Vinci), vitofichera@outlook.com (V. Fichera), luca.tarotto@gmail.com (L. Tarotto), piero_trovato@hotmail.it (P. Trovato), M.PrevedoniGorone@smatteo.pv.it (M.S. Prevedoni Gorone).

https://doi.org/10.1016/j.ejro.2019.02.002
Received 26 January 2019; Received in revised form 3 February 2019; Accepted 5 February 2019
Available online 14 February 2019

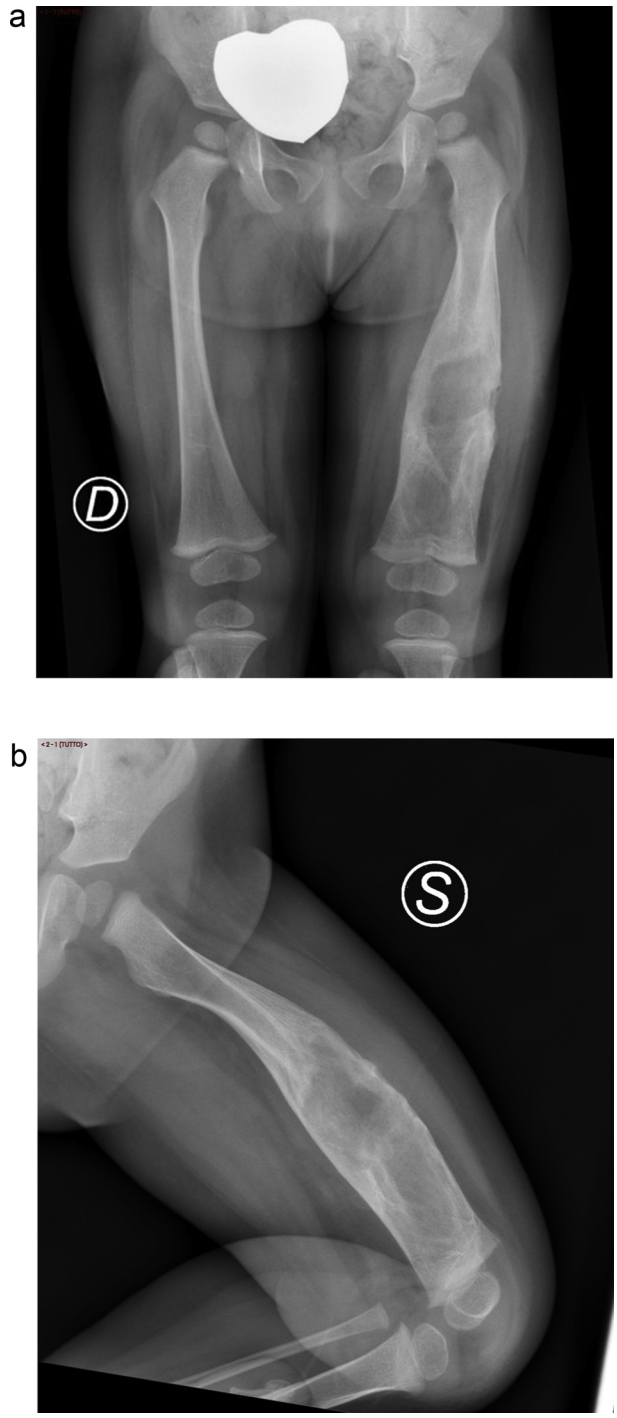

Fig. 1. (a and b) Radiographs demonstrating an expansive multiloculated osteolytic lesion involving the femur, causing a "wine fiasco" bone deformity. The lesion did not spread beyond the growth plate, and no fractures were present.

found to have the following immunophenotype: CD1a+, S100+, CD163+, CD34-, and CD31-. After a second revision of the biopsy by an orthopaedic specialist centre, the diagnosis of LCH masquerading as ABC was confirmed.

Radiological staging of the other bone compartments was then performed, which revealed a single osteolytic lesion of the left zygomatic bone (Fig. 3). This result was confirmed by a face and neck MRI and a whole-body MRI. Pharmacological therapy was started, and a good response was observed for both lesions.

3. Discussion

Langerhans cell histiocytosis (LCH) is a rare disorder of the myeloid precursor cells, characterised by uncontrolled proliferation and accumulation of CD1a+/CD207+ dendritic cells [1]. The incidence is 5–6 cases per 1 million people, and it is more common in children (50–90%) and in males (M:F ratio = 1.2–1.4:1) [1,2].

LCH can be divided into two different forms: single-system, where a single organ is involved with a multifocal or unifocal localisation, which is usually associated with a good prognosis [3]; and multi-system, in which more organs are affected, associated with a better prognosis when the skin, bones, lymph nodes or pituitary gland are involved, but a worse prognosis when the bone marrow, liver, spleen or lungs are involved [4].

The bone is the most commonly affected organ (80%), usually with a unifocal localisation [5,6]. It typically involves the flat bones, with the skull and ribs representing the most frequently involved bones in adults, while the vertebral bodies (especially the cervical part), long bones (the femoris, humerus and tibia, in that order) and jaw are more commonly involved in children [1,7,8]. LCH can be asymptomatic or it can manifest with different signs or symptoms according to the organ involved. The most common symptoms are pain, bone swelling, a cutaneous rash and lymphadenopathy, followed by splenomegaly, hepatomegaly, neutropenia, anaemia, thrombocytopenia, respiratory insufficiency and haemorrhagic diarrhoea [1].

When LCH affects the facial bones or the base of the skull, there is an increased risk of intracranial extension of the disease, with the possibility of developing insipidus diabetes or neurological defects. Alternatively, if it occurs in the vertebral body, it can cause an advanced compression fracture, representing the most common cause of vertebra plana in children [4]. Lesions in the long bones are associated with an increased risk of bone fracture [9].

Treatment depends on the extent of the disease, and varies from observation alone, oral or intravenous medication, to surgery or radiation therapy [4].

Aneurysmal bone cysts are benign, expansive, lytic bone lesions that cause cortical bone thinning, without exceeding it. These lesions produce cavities within the bone that fill with blood, and these cavities are lined by proliferative fibroblasts, giant cells and trabecular bone. The incidence is 1.4 cases per 1 million people, and it is more common in children and young adults (90%) and in females (M:F ratio = 1:1.16). The aetiology of ABC is unknown. Different forms of ABC have been described:

- primary or "classical" ABC, which is considered an independent neoplasia because it is correlated with a specific genetic translocation t(16;17) (q22;p13) involving the gain-of-function of TRE17/USP6 (ubiquitin-specific protease USP6 gene);
- secondary (30% of cases), which is associated with another lesion such as chondroblastoma, giant cell tumour, chondromyxoid fibroma, non-ossifying fibroma, osteosarcoma or fibrous dysplasia; these forms are not considered to be neoplastic because translocation or genetic aberrancy are not known;
- solid ABC or giant cell reparative granuloma; and
- soft-tissue aneurysmal cyst.

The most common sites include the metaphysis of long bones, like the femur, tibia and fibula, followed by the bones of the upper extremities. However, it can also be present in the spine, pelvis, clavicle, feet and fingers. ABC can be asymptomatic, but it can also cause pain, which is its main revealing symptom, in addition to swelling in the proximity of the affected bone. Due to aggressive erosion of the bony architecture, ABC can lead to impending or pathologic fracture, which can acutely worsen symptoms. In the spine, lesions may cause neurological deficits secondary to the mass effect impinging on the spinal cord or exiting nerve roots. As ABC commonly manifests in the

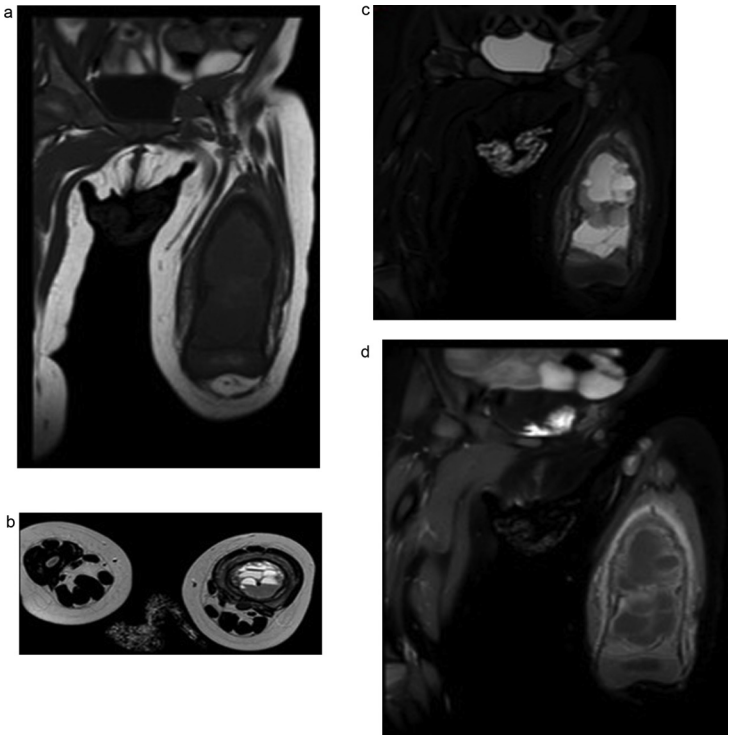

Fig. 2. (a) Coronal TSE T1 image showing a lesion in the femur, characterised by a low intensity, non-homogeneous signal. (b) Axial TSE T2 and (c) coronal STIR images demonstrating an expansive mass with large cavities with fluid-fluid levels. (d) Following administration of gadolinium, coronal T1 SPIR showed slight enhancement of the septa, with no signs of infiltration of adjacent tissues.

paediatric population, growth plates can be affected, leading to limb deformity and length discrepancies.

The standard for treatment remains curettage and grafting to fill the bone void. When ABCs are found in anatomic locations where surgery would cause significant morbidity, they are most often treated with embolization or radiotherapy and, increasingly, medical management with denosumab. The risk of recurrence is very low.

Reports of secondary ABC occurring in LCH are extremely rare in the literature, as this has only been reported twice. Roncaroli et al. [15] and Krishnan [16] described the presence of a skull lesion with typical radiological features of ABC in two different cases. Only the histological examination revealed the presence of cells suggestive of LCH. To our knowledge, this is the first case of LCH masquerading as ABC in the femur. Krishnan pointed out that the prevalence of LCH in ABC is underestimated, possibly due to the old colour-based immunohistochemical techniques used or the minimal presence of typical cells in the biopsy specimen, in addition to the few cases in the literature and, consequently, limited knowledge of this condition.

The evaluation includes **X-ray** as the initial diagnostic exam for LHC and ABC. X-ray is performed to study the characteristics of LHC bone and it is also considerate an accurate exam for staging the disease. Lesions of the skull are characterised by osteolytic foci with well-defined borders (“punchet out”) and no sclerotic rim, and asymmetric destruction of the inner and outer cortices results in a bevelled-edge or a double-contour appearance [10]. Skull lesions can be multiple, and they can converge to form one lesion with a “geographic skull” aspect [9]. The presence of “floating teeth” in the mandible or maxilla, caused by destruction of the alveolar ridge, should suggest a diagnosis of LCH, particularly when the patient is a child and when other skull lesions are present [11]. In the long bones, LCH involves the diaphysis or the metaphysis and respects the growth plates. Lesions have a radiological appearance of aggressive, endosteal calloping, periosteal reaction, cortical thinning and intracortical tunnelling, and an associated soft tissue mass may be present [9]. On X-ray, ABCs classically appear as eccentrically located radiolucent cystic lesions circumscribed by a thin sclerotic margin. Trabeculations within the lesion can impart a multilocular appearance, which has been colloquially described as a “soap bubble appearance”. The cortex is thinned but generally intact, with no periosteal reaction. The best imaging technique to delineate the lesion in LCH is done by the Computed tomography (CT) which allows to assess the degree of trabecular and cortical destruction in areas at risk of impending fracture. It also provides important details for biopsy and surgical planning [6]. Otherwise CT in ABC is less sensitive than MRI and shows fluid levels in only a third of cases. CT may show the cavitary-septa structure, and can define the osseous borders of the lesion. In complex regions such as the spine or pelvis, CT can provide a lesion map and assist in determining fracture risk and the assessment of filling after treatment. The previously mentioned features such as the “soap bubble” appearance and fluid-fluid levels are not pathognomonic for ABCs, as other lesions such as unicameral bone cysts, giant cell tumours, osteoblastoma and telangiectatic osteosarcoma can also present these features. Thus, other differential diagnoses include osseous haemangioma and giant cell reparative granuloma.

Finally the Magnetic resonance imaging (MRI) is a non-invasive technique with high-contrast resolution that allows for anatomic evaluation of the bones, soft tissues and nerves that can be infiltrated by the bone lesions [6]. The LCH aspect on MRI is characterised by a low signal intensity on T1-weighted images and a strong heterogeneous signal intensity on T2-weighted images, with enhancement after administration of a gadolinium-based contrast agent. Oedema of the bone marrow and surrounding soft tissue may also be present [9]. For skull lesions, differential diagnoses for single-system LCH include epidermoid and dermoid cysts, and multi-system LCH include lymphoma, leukaemia, multiple myeloma and metastases. Osteomyelitis must also be considered [6,12]. Vertebral lesions should be differentiated from leukaemia, ABC, metastatic neuroblastoma or Ewing sarcoma [9], while long bone lesions should be differentiated from chondromyxoid fibromas, plasmacytomas, metastases, unicameral cysts and ABCs. In adults, multiple myeloma or metastases should be considered [13]. In ABC the Magnetic resonance imaging is the examination of choice to complement X-ray. The typical aspect is an expansive lobular lesion or with septa. ABCs present a non-homogeneous hypointense signal in T1-weighted images, and a hyperintense signal in T2-weighted images. Multiple fluid levels may be detected on T2-weighted axial sequences at rest, which represent the layering of blood of varying densities on top of one another. While not specific, these multiple fluid levels are highly

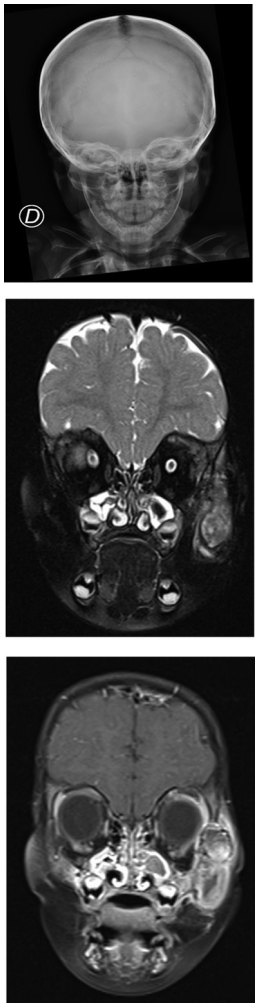

Fig. 3. (a) Radiograph showing an osteolytic lesion of the left zygomatic bone in which context fracture line and bone restructuring can be observed. (b) Coronal TSE T2 FS image demonstrating a large lesion causing cortical erosion and infiltration of the adjacent soft tissues. (c) Following administration of gadolinium, coronal T1 FS images revealed strong, non-homogeneous enhancement of the lesion, and oedema and enhancement of soft tissue can also be observed.

suggestive of ABC. The septa display a hypointense signal in all sequences. Moreover, MRI can reveal perilesional extension and oedema. Gadolinium injection shows enhancement of the cyst walls and internal septa.

The definitive diagnosis for both ABC and LCH is confirmed by histopathological examination and incisional biopsy represents the current gold standard for diagnosis [14].

4. Conclusion

This case, together with other previous cases, suggest that if a patient presents with a rapidly growing bone mass, malignant bone lesion or secondary ABC should be considered. The presence of lesions with ABC-like radiographic findings in bones that are also typical sites for LCH should be submitted to immunohistochemical analysis (CD1a, S100 and Langerin stains) to test for LCH involvement.

X-ray is the first-line radiological examination for the diagnosis of bone LCH and ABC, and it still remains the technique of choice for staging in patients with suspicion of LCH. Contrast-enhanced MRI is the examination of choice to complement X-ray. However, whole-body MRI is becoming increasingly important in the evaluation of extraskeletal and skeletal LCH lesions because it is a radiation-free imaging modality. The exact role of MRI in the diagnostic algorithm of LCH requires further investigation [6,17]. CT is not routinely used in children due to the radiation exposure.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights

This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] M. Jezierska, J. Stefanowicz, G. Romanowicz, W. Kosiak, M. Lange, Langerhans cell histiocytosis in children—a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment, Postepy Dermatol. Alergol. 35 (1) (2018) 6–17.
[2] M.R. DiCaprio, T.T. Roberts, Diagnosis and management of Langerhans cell histiocytosis, J. Am. Acad. Orthop. Surg. 22 (10) (2014) 643–652.
[3] A. Morimoto, Y. Ishida, N. Suzuki, et al., Nationwide survey of single-system single site Langerhans cell histiocytosis in Japan, Pediatr. Blood Cancer 54 (1) (2010) 98–102.
[4] Board PPTE, Langerhans Cell Histiocytosis Treatment (PDQ®) [Internet], National Cancer Institute (US), 2009 Accessed 26 August 2018 https://www.ncbi.nlm.nih.gov/books/NBK65799/.
[5] O. Abla, R.M. Egeler, S. Weitzman, Langerhans cell histiocytosis: current concepts and treatments, Cancer Treat. Rev. 36 (4) (2010) 354–359.
[6] S. Khung, J.-F. Budzik, E. Amzallag-Bellenger, et al., Skeletal involvement in Langerhans cell histiocytosis, Insights Imaging 4 (5) (2013) 569–579.
[7] V. Merglová, D. Hrušák, L. Boudová, P. Mukenšnabl, E. Valentová, L. Hostička, Langerhans cell histiocytosis in childhood—review, symptoms in the oral cavity, differential diagnosis and report of two cases, J. Craniomaxillofac. Surg. 42 (2) (2014) 93–100.
[8] I. Ghanem, V.T. Tolo, P. D'Ambra, M.H. Malogalowkin, Langerhans cell histiocytosis of bone in children and adolescents, J. Pediatr. Orthop. 23 (1) (2003) 124–130.
[9] J. Zaveri, Q. La, G. Yarmish, J. Neuman, More than just Langerhans cell histiocytosis: a radiologic review of histiocytic disorders, Radiographics 34 (7) (2014) 2008–2024.
[10] M.A. Stull, M.J. Kransdorf, K.O. Devaney, Langerhans cell histiocytosis of bone, Radiographics 12 (4) (1992) 801–823.
[11] N. D'Ambrosio, S. Soohoo, C. Warshall, A. Johnson, S. Karimi, Craniofacial and intracranial manifestations of Langerhans cell histiocytosis: report of findings in 100 patients, Am. J. Roentgenol. 191 (2) (2008) 589–597.
[12] V. Chaudhary, S. Bano, R. Aggarwal, et al., Neuroimaging of Langerhans cell histiocytosis: a radiological review, Jpn. J. Radiol. 31 (12) (2013) 786–796.
[13] Y.S. Song, I.S. Lee, J.H. Yi, K.H. Cho, D.K. Kim, J.W. Song, Radiologic findings of adult pelvis and appendicular skeletal Langerhans cell histiocytosis in nine patients, Skeletal Radiol. 40 (11) (2011) 1421–1426.
[14] PDQ Pediatric Treatment Editorial Board, Langerhans cell histiocytosis treatment (PDQ®): health professional version, PDQ Cancer Information Summaries [Internet], National Cancer Institute (US), Bethesda, MD, 2002 Accessed 26 August 2018 http://www.ncbi.nlm.nih.gov/books/NBK65799/.
[15] F. Roncaroli, A. Consales, E. Galassi, B. Bernardi, B. Valeri, Occipital aneurysmal bone cyst secondary to eosinophilic granuloma, Pediatr. Neurosurg. 35 (2) (2001) 103–106.
[16] C. Krishnan, Langerhans cell histiocytosis masquerading as aneurysmal bone cyst, J. Clin. Oncol. 29 (24) (2011) e688–e690.
[17] D. Cafagna, G. Rubini, F. Iuele, et al., Whole-body MR-DWIBS vs. [18F]-FDG-PET/CT in the study of malignant tumors: a retrospective study, Radiol. Med. (Torino) 117 (2) (2012) 293–311.