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Short communication

Acrodermatitis chronica atrophicans in children: Report on two cases and review of the literature

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ABSTRACT

Acrodermatitis chronica atrophicans is a late manifestation of European Lyme borreliosis and is characterized by high levels of borrelial IgG antibodies, slowly expanding skin redness usually beginning on distal parts of extremities, and corresponding histologic findings. It very rarely develops in children. The main prerequisite for the diagnosis is clinical suspicion. In the present article we report on two children with acrodermatitis chronica atrophicans and on the findings of a PubMed literature search on acrodermatitis chronica atrophicans in childhood, published in the past three decades.

1. Introduction

Acrodermatitis chronica atrophicans (ACA) is a cutaneous manifestation of late Lyme borreliosis (LB), seen almost exclusively in Europe. It develops months to years after infection with *Borrelia burgdorferi* sensu lato and is most commonly caused by *Borrelia afzelii* (Asbrink and Hovmark, 1985; Picken et al., 1998; Ružić-Sabljić et al., 2002; Strle and Stanek, 2009). Although ACA may be preceded by erythema migrans or other manifestations of LB, it usually develops as the first and the only sign of the disease. The skin manifestations are typically located on the extremities and are more frequently seen in female than in male patients. Affected persons are usually over 50 years of age (Asbrink, 1993; Müllegger, 2004; Ogrinc et al., 2017; Stanek and Strle, 2003; Stanek et al., 2012; Strle et al., 2013). The proportion of ACA among adult patients with LB is < 4% (Berglund et al., 1995; Strle and Stanek, 2009) and it occurs only exceptionally in childhood.

We report on two children with ACA and on the findings of a PubMed literature search on ACA in childhood, published in the past three decades.

2. Case reports

2.1. Case 1

A 13-year-old previously healthy girl was referred to our department in March 2006. She had noticed a bluish-red discoloration of the distal part of her left foot in August 2005. During the following months, the skin lesion spread to the left instep and became more intensively colored. The girl denied local or constitutional symptoms. She recalled two tick bites in 2004, one on the right leg and the other behind the left ear; no erythema migrans was observed at the site of the bites.

In February 2006 she visited a local dermatologist. No precise diagnosis was made; however, because of the skin lesion and the presence of borrelial IgG antibodies in serum, the girl was prescribed azithromycin (250 mg twice daily for the first day, followed by 250 mg once daily for the following 4 days). The skin lesion persisted. Examination in March 2006 found a red-bluish discoloration of the distal two-thirds of the left foot, without accompanying edema and with a normal-looking structure of the skin. Inadequately treated erythema migrans was suspected initially and the girl was re-treated with amoxicillin (500 mg three times daily for 14 days). All routine laboratory findings were within normal ranges. Serum borrelial antibody determination in indirect immunofluorescence assay with a local *B. afzelii* human isolate as antigen was highly positive for IgG antibody (1:4096) but was negative for IgM antibodies. Cultures of skin and blood samples for *B. burgdorferi* sensu lato were negative. Histologic examination of the skin lesion showed superficial and deep, mainly perivascular, mild infiltration with lymphocytes and plasma cells, mild skin atrophy and focal dermal loss of elastic fibers. A diagnosis of ACA

Abbreviations: ACA, acrodermatitis chronica atrophicans; LB, Lyme borreliosis

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was established and the girl received a course of intravenous ceftriaxone (2 g daily for 3 weeks). The skin lesion disappeared entirely one year later. On a follow-up visit two years after the ceftriaxone treatment the girl was completely healthy, and in indirect immunofluorescence assay the IgG titer had declined to borderline values (1:256).

2.2. Case 2

A 15-year-old girl, referred to our LB outpatient clinic in March 2015, became aware of a red discoloration of the skin in the left knee region in spring 2013. During the following 12 months the redness spread down toward the left foot and gradually turned to a bluish color. In June 2014, a bluish-red discoloration of the dorsal part of her right hand also appeared, which slowly expanded up to the elbow. Two years after the beginning of the illness, she visited our LB outpatient clinic. The girl did not have any underlying illness. She reported having had approximately two tick bites per year, but did not remember a bite at the affected body sites and did not recall redness suggestive of erythema migrans. She had no local symptoms. However, during the few months before the visit she experienced fatigue, difficulties in concentration, and spells of irritability. She also suffered from intermittent wrist, knee, and ankle pains lasting from a few days to two weeks. On physical examination, skin discoloration was visible on the left lower leg distal from the knee, and on the dorsal part of the right hand, forearm and elbow with mild edema but without induration or atrophy (Fig. 1A and B). All routine blood and CFS laboratory tests were within normal ranges. An indirect chemiluminescence immunoassay (LIAISON®, Diasorin, Italy) using the VlsE and OspC recombinant antigen disclosed the presence of borrelial serum IgM antibodies (33.4 IU/ml; borderline values 18–22 IU/ml) and high levels of IgG antibodies (1826 IU/ml; borderline values 10–15 IU/ml). Cerebrospinal fluid samples were negative for IgM antibodies (0.07 IU/ml) but positive for IgG (29.1 IU/ml); calculation according to Reiber and Peter (2001) did not indicate intrathecal synthesis of specific antibodies. Histologic examination of skin specimens from the dorsum of the right hand and left foot showed moderate to intensive perivascular interstitial infiltration with numerous lymphocytes, plasma cells, macrophages, and single eosinophilic granulocytes; thickening of the collagen bundles and loss of elastic fibers were also present (Fig. 1C–E). Skin specimens from hand and foot were cultured in MKP medium (Ružić-Sabljić et al., 2002) and borreliae were isolated from both biopsy sites. Typing with pulsed-field gel electrophoresis (Ružić-Sabljić et al., 2002) and polymerase chain reaction (Postic et al., 1994) revealed the presence of *B. afzelii*. The patient was treated with doxycycline (100 mg twice daily for 28 days). Skin biopsies at the sites of the first procedures were repeated 3 months after antibiotic treatment and were culture negative for borreliae. The skin lesions on the right forearm and elbow disappeared approximately 12 months after treatment and those on the right hand 6 months later. The bluish-red discoloration on the left leg persisted longer, slowly becoming a normal skin color from the proximal to the distal part of the extremity. At examination 2 years after antibiotic treatment only a slight hyperpigmentation of the left foot was still visible; tests for borrelial IgM antibodies were negative although IgG antibodies were still present (685.6 IU/ml).

3. Discussion

ACA is a late manifestation of LB. It begins as skin redness, usually on the dorsal part of the foot or hand, and very slowly expands, becoming more intensively bluish and often accompanied by local edema. After several months to years the edema disappears and the skin gradually becomes more and more atrophic. The histopatologic pattern of ACA is not diagnostic per se, but characteristic enough to alert the experienced pathologist. Histologically, infiltrations with lymphocytes, plasma cells, and histiocytes are seen in the initial edematous stage; in the late stage, atrophy of the dermis, accompanied by the loss of elastic fibers and pilosebaceous follicles, variable epidermal atrophy, and

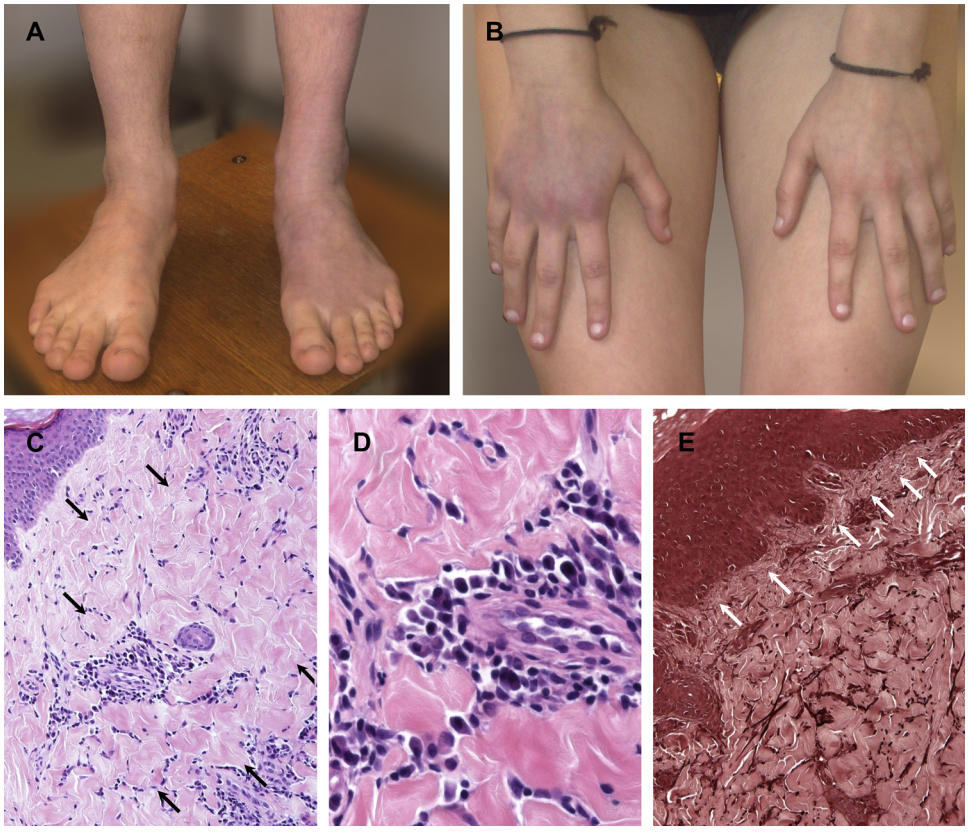

Fig. 1. Case 2. Acrodermatitis chronica atrophicans of the left lower leg (A) and of the dorsal part of right hand (B). Histologic examination of skin biopsies from the left foot and right hand showed almost identical changes: moderate to intensive perivascular and interstitial infiltration with numerous lymphocytes, plasma cells, and macrophages (C, D), thickening and closely packed eosinophilic collagen bundles of the mid and deep dermis (C; arrows) and loss of elastic fibers of the superficial dermis (E; arrows). Staining: H& E (C, D) and orcein (E).

plasma cell infiltration around dilated dermal vessels are found. Marked fibrosis and/or sclerosis have been reported in 25% of patients with ACA (Asbrink, 1993; Asbrink et al., 1984, 1986a, 1986b, 1993; Brehmer-Andersson et al., 1998). It has been postulated that, in contrast to the majority of other manifestations of LB, ACA does not heal spontaneously (Asbrink and Hovmark, 1988; Steere, 1989). ACA should be considered as a possible diagnosis in a patient with bluish-red discoloration of a limb with or without swelling and/or atrophy (Müllegger, 2004). Differential diagnoses or more often false interpretation of ACA skin lesions on the lower extremities are vascular insufficiency such as chronic venous insufficiency, superficial thrombophlebitis, hypostatic eczema, arterial obliterative disease, acrocyanosis, livedo reticularis, lymphoedema, 'old skin' or chilblains (Stanek and Strle, 2018).

ACA is seen in Europe but not in North America. This geographic disparity has been attributed to the distinct etiology of LB: in North America *B. burgdorferi* sensu stricto is almost the exclusive agent of LB whereas in Europe the main causative agents of the disease are *B. afzelii* and *B. garinii*, and only rarely *B. burgdorferi* sensu stricto. However, although ACA is principally associated with *B. afzelii* infection, *B. garinii* and *B. burgdorferi* sensu stricto have also been isolated from individual patients (Busch et al., 1996; Picken et al., 1998; Ohlenbusch et al., 1996; Rijpkema et al., 1997; Ružić-Sabljić et al., 2000, 2002). The absence of autochthonous ACA in North America and the isolation of *B. burgdorferi* sensu stricto from the skin of some European patients with ACA appear contradictory, but recent research shows that even though North American and European *B. burgdorferi* sensu stricto are genetically alike, they vary in inflammatory potential and clinical presentation of the disease (Cerar et al., 2016).

A reliable diagnosis of ACA requires an appropriate clinical picture, high levels of IgG antibody against *B. burgdorferi* sensu lato, and supportive histologic findings (Asbrink et al., 1984, 1986a, 1986b, 1993; Asbrink and Howmark, 1988; Stanek et al., 2011). Information on the direct detection of borreliae in ACA skin lesions is limited. Isolation rate of *B. burgdorferi* s.l. from skin in adult patients with ACA is up to 30% (Picken et al., 1998). Demonstration of borrelial DNA in skin with PCR is probably more successful (Lenormand et al., 2016), however, a report published 20 years ago (Picken et al., 1997) revealed lower detection rate with PCR (7/43, 16%) in comparison to culture (11/43, 26%).

In 1883, the German physician Buchwald described a diffuse idiopathic skin atrophy (Buchwald, 1883) that was subsequently named ACA by Herxheimer and Hartmann in 1902 (Herxheimer and Hartmann, 1902). Thus, ACA was known in Europe 100 years before the recognition of LB in 1983 (Burgdorfer et al., 1983; Steere et al., 1983). As reviewed by Müllegger et al. (1996), publications from the end of the 19th and first half of the 20th century indicate that the large majority of patients with ACA were adults, most often elderly women, that ACA was rarely found in young adults and children, and that the diagnosis of ACA was based on clinical findings and – in some articles – further substantiated by skin histology. Following the recognition that ACA is a manifestation of LB, information on ACA in children has been very limited, most probably because of the rarity of this condition. Namely, of 592 patients diagnosed with ACA (all fulfilling clinical, serologic, and histologic criteria) at our LB outpatient clinic in Ljubljana, Slovenia, in the period 1991–2015, only six (1%) were under 21 years old (Ogrinc et al., 2017) and only two (0.3%) were under 18 (the two children presented here). Findings of the PubMed literature search also suggest that ACA is an exceptionally rare manifestation of LB in childhood: only seven reports comprising nine children with ACA have been published in the past three decades, i.e., after the discovery that ACA is a manifestation of LB (Andres et al., 2010; Brzonova et al., 2002; Gellis et al., 1991; Menni et al., 1996; Müllegger et al., 1996; Mutasim, 2012; Nadal et al., 1988; Zalaudek et al., 2005). Furthermore, a reliable diagnosis of ACA according to current requirements, i.e. based on clinical, serologic, and histologic criteria, has been made in solely six children. Consequently, as shown in Table 1 information on ACA in children is very limited and somewhat heterogeneous. For example, skin culture for borreliae has been attempted in only three cases and was negative in all of them (Brzonova et al., 2002; Nadal et al., 1988), whereas polymerase chain reaction gave a positive result in 4/6 cases (Andres et al., 2010; Brzonova et al., 2002; Menni et al., 1996; Müllegger et al., 1996; Zalaudek et al., 2005), with *B. afzelii* identified for the first time in one child with ACA (Müllegger et al., 1996). Treatment approaches have been considerably diverse: patients were treated with penicillin G, penicillin V, amoxicillin, cefuroxime, tetracycline, doxycycline and/or ceftriaxone for 10 days to 17 weeks, and were often retreated, probably because of the slow resolution of the skin lesions that usually took at least several months. Although no studies on the treatment of ACA in children have been published, some general rules on antibiotic therapy, including its duration, may still apply. Since antibiotics act on etiologic agents (borreliae) but do not directly improve inflammation and tissue damage, the duration of treatment need not (and should not) be guided by the persistence of ACA skin lesions. For children it appears, for the time being, that the most logical approach would be to adjust the recommendations for ACA treatment in adults (Stanek et al., 2012), including the duration of antibiotic treatment to up to 4 weeks, adjusting the dosage and avoiding use of doxycycline in children under 8 years of age.

The limited information on childhood ACA does not permit reliable comparison of findings in children and adults. Nevertheless, it seems that i) female predominance is also present in children: 8/11 (72.7%) patients (9 reported previously, 2 presented here) were girls, which is comparable to the sex ratio in Slovenian adult patients with ACA diagnosed in the period 1991–2015 where 386/590 (65.4%) were females (Ogrinc et al., 2017), and that ii) in children, previous manifestations of LB are rare: none of the children shown in Table 1 reported having had EM or any other manifestation of LB prior to ACA, whereas in a series of adult patients with ACA about 20% recalled previous erythema migrans (Asbrink, 1993; Asbrink et al., 1986a, 1986b; Asbrink and Hovmark, 1988). In addition, comparison of the two age groups shows that iii) the location of the ACA skin lesions is on the extremities in both children and adults; iv) ACA is associated with high levels of borrelial IgG antibodies that persist for several months to years after antibiotic treatment; v) patience is needed when assessing the effectiveness of antibiotic treatment (usually at least 6 months is necessary to achieve improvement), and vi) the duration of ACA skin lesions prior to diagnosis is several months to years, suggesting diagnostic difficulties, which – due to the rarity of ACA in childhood – might be even more pronounced in children than in adults.

The diagnosis of ACA was delayed in the two cases presented in this report. In the 13-year-old girl the skin lesion was initially not recognized at all, and was later estimated as erythema migrans by inexperienced physicians; the lesion lasted for 7 months before proper diagnosis and treatment. In our second case, ACA was diagnosed only 2 years after the onset of the skin lesion. In this 15-year-old girl, in addition to a typical clinical presentation, appropriate histologic findings, and high serum levels of borrelial IgG antibodies, the etiologic diagnosis was further substantiated by isolation of *B. afzelii* from skin lesions, representing the first published case of isolation of borreliae from an ACA skin lesion in a child.

4. Conclusion

The main aim of this report is to alert pediatricians and other physicians involved in the treatment of children that although ACA is rare it may develop in childhood and that the diagnosis is relatively simple if there is appropriate basic knowledge that allows clinical suspicion.

Table 1
Findings of a PubMed literature search on acrodermatitis chronica atrophicans in children (cases 1–9) and own results (cases 10 and 11).

Case no. Age Sex	Tick bite	Clinical findings			Laboratory findings[a]	Diagnosis confirmation			Treatment	Outcome[b]	Reference/ Country
		Duration[c]	Location/ Skin color/ Edema/ Atrophy[a]	Associated symptoms[d]		Borrelia serology[e]	Histology	Borrelia culture/ PCR			
1. 10 y boy	Yes (1 y[f])	Few w	Right lower leg/ Livid/ Yes, in some areas/ No[g]	None	ESR: 22; WBC[h]: normal	IFA IgM NA IgG ↑↑ pos At 6 m: IgM NA IgG ↑↑ pos	Thin epidermis, strongly pigmented stratum basale, patchy perivascular lymphocytic, plasma cell and histiocytic infiltration	Neg/ ND	PEN G 12 MU/m^2/ day iv, 28 days	At 1 w: resolution of edema At 6 m: complete resolution	Nadal et al. (1988)/ Switzerland
2. 12 y boy	No	1 y	Left leg/ Violet/ Yes (left thigh)/ Yes (in some areas)	None	ESR: 20; WBC[h]: normal	IFA IgM NA IgG ↑↑ pos At 6 m: IgM NA IgG ↑↑ pos	Pronounced edema of the corium, patchy perivascular infiltrates mainly with lymphocytes	Neg/ ND	PEN G 12 MU/m^2/ day iv, 28 days	At 1 w: improvement of edema At 6 m: complete resolution	Nadal et al. (1988)/ Switzerland
3. 12 y girl	No	2 y	Hands, wrists and ankles/ Blue-grey/ No/ Yes	None	ANA, RF, VDRL and TPHA: neg	IB IgM NA IgG pos (ELISA neg) Follow-up: NA	Mild dermal fibrosis, few perivascular mononuclear inflammatory cells; silver staining (Warthin-Starry) revealed visible spirochetes before and the absence of visible spirochetes after antibiotic treatment	ND/ ND	PEN G 12 MU/day iv, 14 days; → TET 500 mg qid po, 14 days	No improvement[i]	Gellis et al. (1991)/ USA
4. 11 y boy	No	4 m	Back of the hands and feet, wrists, right scapular region, neck/ Erythematous-brownish/ Yes/ Yes – mild	None	NA	IFA IgM NA IgG pos At 6 m: IgM NA IgG titer declined[j]	ND	ND/ Pos	PEN G 2 MU/day iv, 20 days	Shortly after therapy: healing of erythematous lesions At 6 m: persistence of atrophic lesions	Menni et al. (1996)/Italy
5. 11 y girl	Yes (1 y[f])	3 y	Left leg/ Bluish-red patches/ Yes/ Yes – slight	None	WBC, BCh: normal	ELISA IgM neg IgG ↑↑ pos Follow-up[h]: IgM neg IgG ↑↑ pos	Slightly atrophic epidermis, perivascular and interstitial infiltrate (lymphocytes, plasma cells, histiocytes)	ND/ Pos (*Ba*)	CRO 2 g/day iv, 14 days	Marked improvement[i]	Muelleger et al. (1996)/Austria
6. 11 y girl	Yes (3 y[f])	2 y	Legs and arms, extending to the chest/ Bluish-red/ Yes/ Yes	Arthralgia, fatigue, skin dryness, weight gain	WBC, BCh: normal; ANA 1:80; ↑ IgM and IgG; IgA: normal; VDRL and TPHA: neg	ELISA and IB IgM neg IgG ↑↑ pos At 5 m: IgM neg IgG pos	Edema of the dermis, dense lymphocytic infiltration, rich in plasma cells and histiocytes	Neg/ Pos	CRO 2 g/day iv, 28 days	At 9 m: complete resolution	Brzonova et al. (2002)/Czech Republic
7. 15 y girl	No	6 y	Left knee and pretibial region, elbows and ulnar regions/ Bluish red/ Yes/ Yes – marked	Arthralgia (left knee, intermittent)	ESR, CRP, WBC, BCh, ANA, RF: normal; ↑IgG; ↑circulating immune complexes	ELISA and IB IgM neg IgG ↑↑ pos At 6 m: IgM neg IgG ↑↑ pos	Atrophy of the epidermis, superficial and deep, perivascular and interstitial dermal infiltrate with lymphocytes, histiocytes, plasma cells	ND/ Neg	DOX 100 mg bid po, 42 days	At 6 m: complete resolution of inflammatory skin changes, persistence of atrophy	Zalaudek et al. (2005)/Austria
8. 8 y girl	Yes (2 y[f])	1 y	Right leg/ Bluish-red Yes/ No	Paresthesia (right leg and toes), arthritis (right knee, intermittent)	NA	ELISA and IB IgM ↑↑ pos IgG ↑↑ pos After therapy[i]: IgM pos IgG ↑↑ pos	Intense edema of the dermis, perivascular lympho-histiocytic and plasma cell infiltration	ND/ Pos	CRO 2 g/day iv, 14 days; → CXM 500 mg bid po, 10 days	Slow resolution[i]	Andres et al. (2010)/Germany

(*continued on next page*)

Table 1 (*continued*)

Case no. Age Sex	Tick bite	Clinical findings			Laboratory findings[a]	Diagnosis confirmation			Treatment	Outcome[b]	Reference/ Country
		Duration[c]	Location/ Skin color/ Edema/ Atrophy[a]	Associated symptoms[d]		Borrelia serology[e]	Histology	Borrelia culture/ PCR			
9. 10 y girl	No	18 m	Right leg, right trunk/ Erythematous whitish patches/ No/ Yes	None	NA	ELISA and IB IgM neg IgG ↑↑ pos After therapy[i]: IgM declined[j] IgG ↑↑ pos	Thickened collagen bundles in reticular dermis, inflammatory infiltration with lymphocytes and some plasma cells	ND/ Neg	CRO 2 g/day iv, 28 days; → PEN G 5 MU tid, 6 days; → PEN V 1.2 MU tid, 90 days	Slow resolution of inflammatory skin lesions, persistence of atrophy[i]	Andres et al. (2010)[k]/Germany
10. 13 y girl	Yes (1 y[f])	7 m	Left foot and instep/ Bluish-red/ No/ No	None	WBC, BCh: normal	IFA IgM neg IgG ↑↑ pos At 2 y: IgM neg IgG pos	Mild skin atrophy and focal dermal degeneration of elastic fibers, superficial and deep, mainly perivascular infiltration with lymphocytes and plasma cells	Neg/ ND	AZM 1.5 g, → AMX 500 mg tid, 14 days; →CRO 2 g/day, 21 days	At 1 y: complete resolution	Current report/ Slovenia
11. 15y girl	No	2 y	Left knee, shank and feet; right hand and forearm/ Bluish-red/ Yes/ No	Arthralgia, concentration impairment, irritability	WBC, BCh: normal,	ELISA IgM pos IgG ↑↑ pos At 2 y: IgM neg IgG pos	Sclero-inflammatory changes with intensive perivascular and interstitial infiltration with lymphocytes, plasma cells and macrophages	Pos (*Ba*)/ ND	DOX 100 mg bid, 28 days	At 18 m: complete resolution on right hand At 2 y: almost complete resolution on left leg	Current report/ Slovenia

Legend: no., number; y, year; w, week; ESR, erythrocyte sedimentation rate; WBC, white blood cells; IFA, indirect immunofluorescent assay; ↑↑, highly elevated; NA, not available; neg, negative; ND, not done; PEN G, penicillin G; m, month; ANA, antinuclear antibodies test; RF, rheumatoid factor; VDRL, Venereal Disease Research Laboratory test; TPHA, Treponema pallidum haemagglutination test; IB, immunoblot; →, followed by; TET, tetracycline; pos, positive; BCh, blood chemistry; *Ba, Borrelia afzelii;* CRO, *c*eftriaxone*; CRP,* C-reactive protein; DOX, doxycycline; CXM, cefuroxime; PEN V, *p*enicillin V; AZM, azitrhomycin; AMX, amoxicillin.

[a] Findings at the initial visit (when diagnosis was established).

[b] Outcome after antibiotic therapy.

[c] Duration of skin lesions before diagnosis.

[d] In the course of illness before diagnosis.

[e] Borrelia serology at the initial visit and at follow-up.

[f] Before development of skin lesions.

[g] Dry and dystrophic skin over the ankle.

[h] WBC count and differential.

[i] No information on the time of follow-up.

[j] No exact data reported.

[k] In response to the published case report an opinion was expressed that the girl had morphea and not ACA (Mutasim, 2012).

Conflicts of interestsstatement/financial disclosures

Dr. Franc Strle is an unpaid member of the steering committee of ESGBOR, the ESCMID Study Group on Lyme Borreliosis.

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