Cutaneous vasculitis and reactive arthritis following respiratory infection due to *Chlamydia pneumoniae*: Report of a case

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ABSTRACT

Unlike Chlamydia trachomatis *and* C. psittaci, *the association of* C. pneumoniae *infection with immunological complications, such as reactive arthritis (ReA) or erythema nodosum (EN) has been rarely reported. Here we present the case history of a patient with* C. pneumoniae *community acquired pneumonia (CAP) who subsequently developed a ReA and a cutaneous vasculitis.*

A 45-year-old HLA B27 negative male developed an asymmetric and additive arthritis and a cutaneous leukocytoclastic vasculitis with IgM and complement papillary deposition along hypodermic vessel walls about three weeks after the onset of respiratory symptoms. The diagnosis of chronic Chlamydia pneumoniae *infection was based on serology and PCR. Cultural and serological investigations for other infectious agents commonly involved in ReA were negative.*

This is the first report on the occurrence of two immune-based complications, associated to Chlamydia pneumoniae *infection. Therefore, since this infection is very common in our population, although often asymptomatic, should be systematically considered as a common causative agent of ReA and of vasculitis.*

Case report

A 45-year-old man,heavy smoker, presented with a two week history of hoarseness, dry cough, fatigue and fever. On admission (December 1999) the patient had a low grade fever, dry cough, left-sided pleuritic chest pain and painful erythematous nodules involving arms, hands and trunk. Chest radiograph showed nodular infiltrates in the left lower lobe and apical bilateral sclerosis as a result of a previous tuberculosis. White blood cell (WBC) count was 10,550 cells/mm^3 (with 70% neutrophils, 19% lymphocytes, 11% monocytes). Erythrocytes sedimentation rate (ESR) was 34 mm/h and C-reactive protein 2.4 mg/dl. All other blood tests resulted within normal range including liver and renal functions, serum anti nuclear antibodies, cytoplasmic-pattern antineutrophil cytoplasmic autoantibodies (ANCA), and perinuclear-pattern ANCA.

The reaction size of tuberculin skin test (PPD 5TU) was 27 mm. High-resolution computed tomography showed micro-nodular infiltrates along peribronchovascular bundles in the antero- and postero-basal segments of the left lower lobe but no hilar adenopathy. At bronchoscopy an acute bronchial inflammation with mucosal erythema and purulent exudates in the left lower

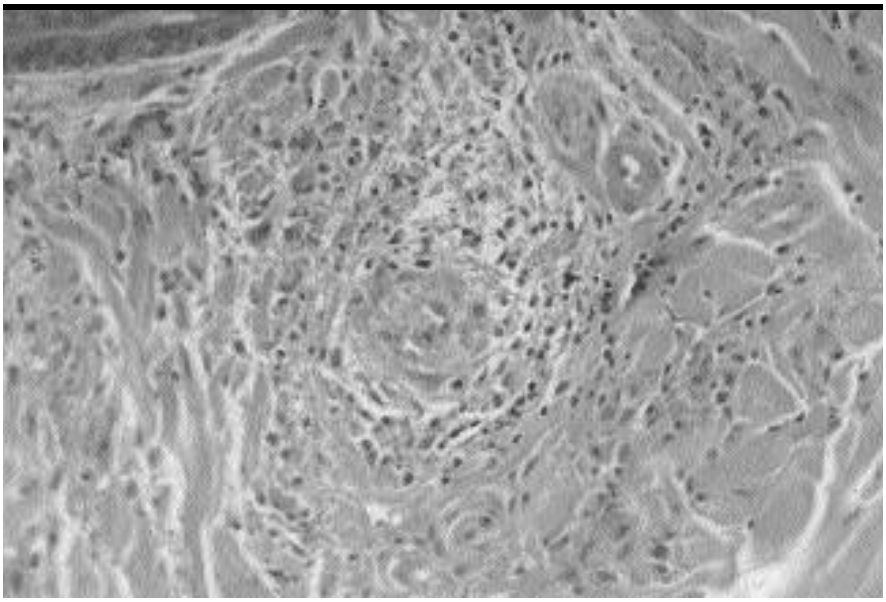

Fig. 1. Histology of cutaneus vasculitis. Note the partial obliteration of the vascular lumen by the leukocyte infiltration.

lobe was detected. Broncho-alveolar lavage (BAL) cytology and microbiology gave normal results. Transbronchial biopsies (TBBs) performed through the left B8 area showed signs of mild interstitial sclerosis. After 6 days the cutaneous nodules became larger and more infiltrated, being suspect for vasculitis or multiform erythema. Histological features of leukocytoclastic vasculitis were found (Fig. 1), and direct immunofluorescence revealed IgM and complement papillary depo-

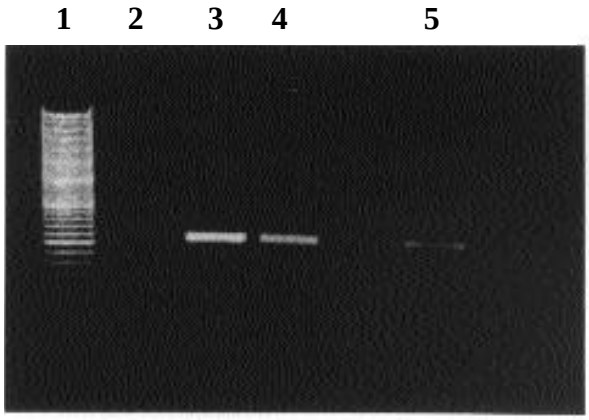

Fig. 2. Gel electrophoresis of nested-PCR for *C. pneumoniae* in broncho-alveolar lavage (BAL) cells and peripheral blood mononuclear cells (PBMC) of the present patient. Positive results have been obtained from PBMC (5) while BAL cells were negative (2). 1. molecular weight; 2. BAL cells obtained from the present patient; 3. positive control; 4. sputum sample obtained from another patient with *C. pneumoniae* pneumonia; 5. PBMC cells obtained from the present patient.

Table I. Review of the literature concerning the association of *C. pneumoniae* infection with reactive arthritis (ReA) and vasculitis.

Authors	Associated disease(s)	Joint involvement	Sex (No. of patients)	Diagnostic criteria of *Chlamydia* infection	Primary infection (site)	Other findings
Gran 1993 (2)	Myocarditis, ReA and EN	Ankles bilateral, wrist monolateral	M (1)	MIF	Lower respiratory	HLA B27 negative
Braun 1994 (3)	ReA	Knee (n=5), elbow (n=1), Achille's tendon (n=1), wrist (n=1)	M=3, F=2 (5)	MIF sera + synovial lymphocyte proliferation to *C. pneumoniae*	Upper (n=1), lower (n=2) respiratory or none (n=2)	HLA B27 positive (n=1) negative (n=1), ND (n=1)
Saario 1994 (4)	ReA	Knees (n=2), ankles (n=3), right forefinger (n=1), shoulder (n=1)	M=3 (3)	MIF (n=1), negative	Upper (n=2) and lower (n=1) respiratory	HLA B27 positive (n=1), negative (n=1), ND (n=1).
Melby 1999 (5)	ReA	Not specified	Not specified (3)	MIF	Not specified	HLA B27 negative (n=3)
Moling 1996 (6)	ReA, pericardial effusion (n=2), conjunctivitis (n=1)	Wrists (n=2), knees (n=1), ankles (n=3), cervical column (n=1), low-back pain (n=1), shoulders (n=2), elbows (n=1) fingers (n=1), subtalar (n=1), enthesopathy (n=1).	M=2, F=2 (4) (4)	MIF	Upper (n=2), lower (n=1) respiratory, not specified (n=1).	HLA B27: positive (n= 1), negative (n=3)
Hannu 1999 (7)	ReA	Knee (n=3), wrist (n=3), ankle (n=4), MTP (n=3), MCP (n=1), low back pain (n=2), enthesopathy (n=3), tenosynovitis (n=2).	M=3, F=1 (4)	MIF	Lower respiratory (n=3), abdominal pain (n=1)	HLA B27 positive (n=3), ND (n=1)
Sundelöf 1993 (9)	Atypical EN, hepatitis, iritis		M (1)	MIF	Meningitis	HLA B27 ND
Kousa 1980 (10)	EN, episcleritis (n=2), conjunctivitis (n=1)	Arthralgia (n=2)	M=4, F=7 (11)	CF (detection of *Chlamydia* spp.)	Lower respiratory (n=6), upper respiratory (n=5),	HLA B27 ND
Marie 1999 (11)	Löfgren's syndrome (bilateral hilaradenopathy, EN and arthritis)		Not specified (3)	MIF		HLA B27 ND
Erntell 1989 (12)	EN		M=1, F=1 (2)	MIF	Lower respiratory (n=2)	HLA B27 ND
Ljungström 1997 (13)	Systemic vasculitis (giant cell arteritis: 1 case). Myocardial infarction (n=2)		M=4, F=1 (5)	MIF	Upper respiratory (n=3), aseptic meningitis (n=1), cerebral arteritis (n=1) Cogan's syndrome (n=1)	
Tauber 1999 (14)	Necrotizing sarcoid granuloma		F (1)	MIF	Lower respiratory (multiple opacities)	
Norman 1999 (15)	Kawasaki disease		M=2, 1 not specified (3)	Immunohistochemical on tissue samples		
Present study	ReA, cutaneous vasculitis, conjunctivitis	Ankle, knee, wrists, MTP, enthesopathy	M (1)	MIF	Upper and lower r espiratory	HLA B27 negative

EN: erythema nodosum, MTP: metatarsophalangeal joint, MCP: metacarpophalangeal, ND: not detected; M: males, F: females; MIF: micro-imunofluorescence; CF: complement fixation.

sition along the hypodermic vessel walls. Three weeks after the onset of respiratory symptoms, an asymmetric and additive arthritis developed involving the right ankle, wrists, metatarsophalangeal joints and left knee. In addition, the patient complained of right enthesopathy and painless conjunctivitis.

In the suspicion of a ReA, serological tests towards several respiratory and gastro-intestinal pathogens were performed (*Chlamydia pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae, Legionella pneumophila, Yersinia spp, Shigella spp,Salmonella spp, Campilobacter spp*) with negative results with the exception of *Chlamydia pneumoniae* serology (micro-immunofluorescence - MIF) with IgG titre = 1:512; IgM titre < 1:16 and IgA titre = 1:16. These findings were consistent with a pattern of reinfection with *C. pneumoniae*. Moreover, a nested polymerase chain reaction (nPCR) for *C. pneumoniae* (193bp region of OMP2-gene) was performed on bronchial aspirate (BA) and peripheral blood mononuclear cells (PBMC) with negative results on the BA and positive results on PBMC (Fig. 2). The patient reached complete clinical resolution in 60 days. He was treated with chlarythromycine, 500 mg twice a day i.v. for 10 days,and subsequently with tetracyclin 100 mg/day orally for 10 days along with diclofenac for arthralgia. *C. pneumoniae* serology after 30 days showed an IgG titre of 1:256 and an IgA titre of 1:16; IgA titre normalized after 60 days. At present (February 2002) the patient is well and stable, no recurrence has been detected.

Discussion

C. pneumoniae is a common pathogen responsible of symptomatic and asymptomatic acute respiratory infections. In addition, clinical and serological evidences of chronic infection have been described for *C. pneumoniae* (1). In the present case the results of serology and the PCR test on PBMC strongly suggested that the patient, as a consequence of a CAP had been chronically infected by *C. pneumoniae*. From the analysis of the literature, and as reported in Table I, acute *C. pneumoniae* infection of the upper or lower respiratory tract seem to play a definite role in triggering ReA (2-7). In all but 2 reported cases (7) serological evidence of chronic infection was not detected. In the pathogenesis of ReA the presence of non-proliferating foreign antigens and/or live but non culturable bacteria is usually thought to play a crucial role by driving a local cellular and humoral response. Concerning *C. pneumoniae*, however, no clear evidence of the presence of this bacteria in the involved joints has been provided apart from a single case described by Braun and colleagues with positive PCR on synovial fluid but without serological evidence of an acute or chronic *Chlamydia pneumoniae* infection (8). In our patient no data are available concerning *Chlamydia pneumoniae* localization in the involved joints, since synovial fluid could not be obtained. Further studies, including the newer molecular diagnostic assays, are therefore needed to assess whether the presence of *C. pneumoniae* in the joint can drive the local immune response causing ReA.

Much less is even known about the role *C. pneumoniae* in the pathogenesis of immune-based vasculitis. In previous reports *C. pneumoniae* infection was associated to either 5 cases of EN (2, 9-12) or 1 case of systemic vasculitis (13) (Table I). No report, however, has been made so far about the simultaneous occurrence of cutaneous vasculitis and ReA following a CAP due to *C. pneumoniae* as we describe. The clinical relevance of this first report on the occurrence of two immune-based complications, is that *C. pneumoniae* infection, which seems to be very common in our population albeit often asymptomatic, should be systematically considered as a causative agent of reactive arthritis and vasculitis.

References

1. PEELING RW, WANG SP, GRAYSTONJT *et al.*: *Chlamydia pneumoniae* serology: interlaboratory variation in microimmunofluorescence assay results. *J Infect Dis* 2000; 181 (Suppl. 3): 426-9.
2. GRAN JT, HJETLAND R, ANDREASSEN AH: Pneumonia, myocarditis and reactive arthritis due to *Chlamydia pneumoniae*. *Scand J Rheumatol* 1993; 22: 43-4.
3. BRAUN J, LAITKO S, TREHARNE J *et al.*: *Chlamydia pneumoniae* - new causative agent of reactive arthritis and undifferentiated oligoarthritis. *Ann Rheum Dis* 1994; 53: 100-5.
4. SAARIO R, TOIVANEN A: *Chlamydia pneumoniae* as a cause of reactive arthritis. *Br J Rheumatol* 1994; 33: 1112-9.
5. MELBY KK, KVIEN TK, GLENNÅS A *et al.*: *Chlamydia pneumoniae* as a trigger of reactive arthritis. *Scand J Infect Dis* 1999; 31: 327-8.
6. MOLING O, PEGORETTI S, RIELLI M *et al.*: *Chlamydia pneumoniae*-reactive arthritis and persistent infection. *Br J Rheumatol* 1996; 35: 1189-90.
7. HANNU T, PUOLAKKAINEN M, LEIRISALO-REPO M: *Chlamydia pneumoniae* as a triggering infection in reactive arthritis. *Rheumatology* 1999; 38: 411-4.
8. BRAUN J, TUSZEWSKI M, EGGENS U *et al.*: Nested polymerase chain reaction strategy simultaneously targeting DNA sequences of multiple bacterial species in inflammatory joint diseases. I. Screening of synovial fluid samples of patients with spondyloarthropathies and other arthritides. *J Rheumatol* 1997; 24: 1092-100.
9. SUNDELÖF B, GNARPE H, GNARPE J: An unusual manifestation of *Chlamydia pneumoniae* infection: meningitis, hepatitis, iritis and atypical erythema nodosum. *Scand J Infect Dis* 1993; 25: 259-61.
10. KOUSA M, SAIKKU P, KANERVA L: Erythema nodosum in chlamydial infections. *Acta Dermatovener (Stockholm)* 1980; 60: 319-22.
11. MARIE I, LECOMTE F, LEVESQUE H *et al.*: Löfgren's syndrome as the first manifestation of acute infection due to *Chlamydia pneumoniae*: Prospective study. *Clin Infect Dis* 1999; 28: 691-2.
12. ERNTELL M, LJUNGGREN K, GADD T *et al.*: Erythema nodosum - manifestation of *Chlamydia pneumoniae* (strain TWAR) infection. *Scand J Infect Dis* 1989; 21: 693-6.
13. LJUNGSTRÖM L, FRANZÉN C, SCHLAUG M, *et al.*: Reinfection with *Chlamydia pneumoniae* may induce isolated and systemic vasculitis in small and large vessels. *Scand J Infect Dis* 1997; 104: 37-40.
14. TAUBER E, WOJNAROWSKI C, HORCHER E, *et al.*: Necrotizing sarcoid granulomatosis in a 14-yr-old female. *Eur Respir J* 1999; 13: 703-5.
15. NORMANN E, NAAS J, GNARPE J *et al.*: Demonstration of *Chlamydia pneumoniae* in cardiovascular tissues from children with Kawasaki disease. *Pediatr Infect Dis J* 1999; 18: 72-3.