Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 43 (1986)
Heft: 2

Artikel: Frequent occurrence of hepatic lesions in boutonneuse fever
Autor: Walker, D.H. / Staiti, A. / Mansueto, S.
DOI: https://doi.org/10.5169/seals-313624

Acta Tropica *43*, 175–181 (1986)

[1] Department of Pathology, University of North Carolina, Chapel Hill, North Carolina, USA
[2] Division of Infectious Diseases, Ospedale Civile di Barcellona, Messina, Italy
[3] Tropical Diseases Clinic, University of Palermo, Palermo, Italy
[4] Institute of Hygiene, University of Palermo, Palermo, Italy

Frequent occurrence of hepatic lesions in boutonneuse fever

D. H. WALKER[1], A. STAITI[2], S. MANSUETO[3], G. TRINGALI[4]

Summary

Seven consecutive Sicilian patients with boutonneuse fever but without clinical symptoms of hepatic disease underwent hepatic biopsy and had similar hepatic lesions. Foci of hepatocellular necrosis were infiltrated with predominantly mononuclear leukocytes. No intact *Rickettsia conorii* were identified in the tissues by immunofluorescence. The apparent high frequency of viscerotropism in boutonneuse fever conforms to the recent observations of severe illness in what had often been described previously as a benign rickettsiosis.

Key words: boutonneuse fever; *Rickettsia conorii;* rickettsia; hepatitis.

Introduction

Human infection by *Rickettsia conorii* has generally been considered a benign rickettsiosis with rare fatality or severe complications. However, numerous recent reports from southern Europe and South Africa have documented that malignant boutonneuse fever (Grillo-Reina et al., 1982; Raoult et al., 1983; Gear et al., 1983; Houvenaeghel et al., 1984; Ruiz et al., 1983, 1984; Pallot et al., 1984; Ruiz et al., 1985) does occur and may result in fatal outcome.

The frequency of boutonneuse fever with visceral as well as cutaneous involvement has been considered to be low. Serum hepatic enzyme concentrations are elevated in boutonneuse fever, and hepatic lesions in biopsy and autopsy specimens have been described (Guardia et al., 1974; Faure et al., 1977; Moncharmont et al., 1981; La Rosa et al., 1981, 1982; Staiti, 1982; Morreale and Mansueto, 1983). There is, however, no consensus about the pathogenesis of hepatic injury. In this report we describe the hepatic findings in biopsy specimens from seven patients with boutonneuse fever who were selected only by their consent to hepatic biopsy.

Correspondence: Dr. David H. Walker, Department of Pathology, University of North Carolina, Chapel Hill, N.C. 27514, USA

Patients and Methods

Patients. During 1983 and 1984, seven patients suspected of having boutonneuse fever were evaluated by Dr. Staiti in Barcellona (Italy) and by Dr. Mansueto in Palermo and consented to hepatic needle biopsy. The clinical and serologic data supporting the diagnosis of infection by *Rickettsia conorii* are presented in Table 1. Two patients had a four-fold rise in titer of antibodies to *R. conorii* documented by indirect immunofluorescent antibody assay (Philip et al., 1976). All seven had serum antibodies to *R. conorii;* five patients, at a titer of 1:160 or higher. All seven had a "tache noire" and fever. Five had a rash as well. Thus, the diagnosis was confirmed in two and very probable in the other five. None had signs or symptoms of hepatic disease.

Laboratory data. Clinical records were reviewed for serum concentrations of lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, and bilirubin.

Liver biopsy histology and immunofluorescence for R. conorii. The hepatic needle biopsies were fixed in neutral buffered 4% formaldehyde, dehydrated in a series of increasing ethanol concentrations, embedded in paraffin, sectioned at 4 μm and stained with hematoxylin-eosin as well as phosphotungstic acid-hematoxylin for fibrin, Verhoeff-Van Gieson for elastic tissue, reticulin, and Perl's Prussian blue for iron. An adjacent serial section was affixed to a microscopic slide with Elmer's glue, deparaffinized in xylene, digested with trypsin, and stained by direct immunofluorescence with a conjugate reactive with *R. conorii* as previously described (Walker and Cain, 1978; Montenegro et al., 1983).

Results

The laboratory data and results of evaluation for presence of hepatic lesions and *R. conorii* are presented in Table 2. The moderate elevations of serum concentrations of LDH, AST, and ALT are compatible with the presence of scattered foci of hepatocellular necrosis, which involved only a small proportion of hepatocytes (Fig. 1). The lobular location of these lesions and the absence of involvement of portal triads is reflected in these results that there were no striking deviations of serum bilirubin and alkaline phosphatase during the acute illness. It is remarkable, nevertheless, that all biopsy specimens contained lesions which appeared to fit the sequence of hepatocellular necrosis followed by focal, predominantly mononuclear, inflammatory reaction. Yet, in no patient were intact immunofluorescent SFG rickettsiae identified in the tissue. Underlying alcoholic or other hepatic injury may have caused fatty change in some of these patients. No other specific lesions indicative of hepatitits B virus infection or alcoholic injury were identified.

Discussion

The investigation confirms the reports of Guardia et al. (1974) and Faure et al. (1977) who described hepatic lesions in patients with boutonneuse fever. We do not believe that the lesions are granulomatous hepatitis, but rather they are foci of hepatocellular necrosis and predominantly mononuclear reaction to the necrosis at sites of infection by *R. conorii.* The lesion differs from a true granuloma in that it is not an aggregate of epithelioid macrophages in contrast to the

Table 1. Clinical and serologic data for Sicilian patients with boutonneuse fever undergoing liver biopsy

	Patient						
	1	2	3	4	5	6	7
Age/Sex	43M	74M	66F	67F	86F	68M	50F
Tache noire	+[1]	+	+	+	+	+	+
Rash	0[2]	+	+	+	+	0	+
Fever	+	+	+	+	+	+	+
Serology							
Acute	160[3]	160	40	N.D.	40	40	320
Convalescent	N.D.[4]	160	N.D.	320	160	N.D.	1280

[1] present
[2] absent
[3] reciprocal of indirect immunofluorescent antibody titer against *R. conorii*
[4] not determined

Table 2. Evaluation of Sicilian patients with boutonneuse fever for hepatic involvement

	Patient						
	1	2	3	4	5	6	7
LDH[1]	120	259	390	251	255	210	N.D.
ALT[2]	15	16	38	10	28	21	85
AST[3]	22	20	30	14	18	18	93
AP[4]	139	N.D.	152	N.D.	290	199	477
GGT[5]	15	51	normal	N.D.	18	N.D.	160
Bil[6]	normal	normal	1.1	0.9	normal	normal	1.0
Day of bx[7]	1	3	6	13	2	2	30
Lesions	+[8]	+	+	+	+	+	+
IF *R. conorii*	0[9]	0	0	0	0	0	0

[1] serum lactate dehydrogenase (reference interval, 100–240 IU/l)
[2] serum alanine aminotransferase (reference interval, 6–31 IU/l)
[3] serum aspartate aminotransferase (reference interval, 6–31 IU/l)
[4] serum alkaline phosphatase (reference interval, 60–170 UI/l)
[5] serum gamma glutamyl transpeptidase (reference interval, 4–18 IU/l)
[6] total serum bilirubin (reference interval, less than 1.0 mg/dl)
[7] number of days after onset of fever
[8] presence of hepatic lesions
[9] absence of immunofluorescent *R. conorii*

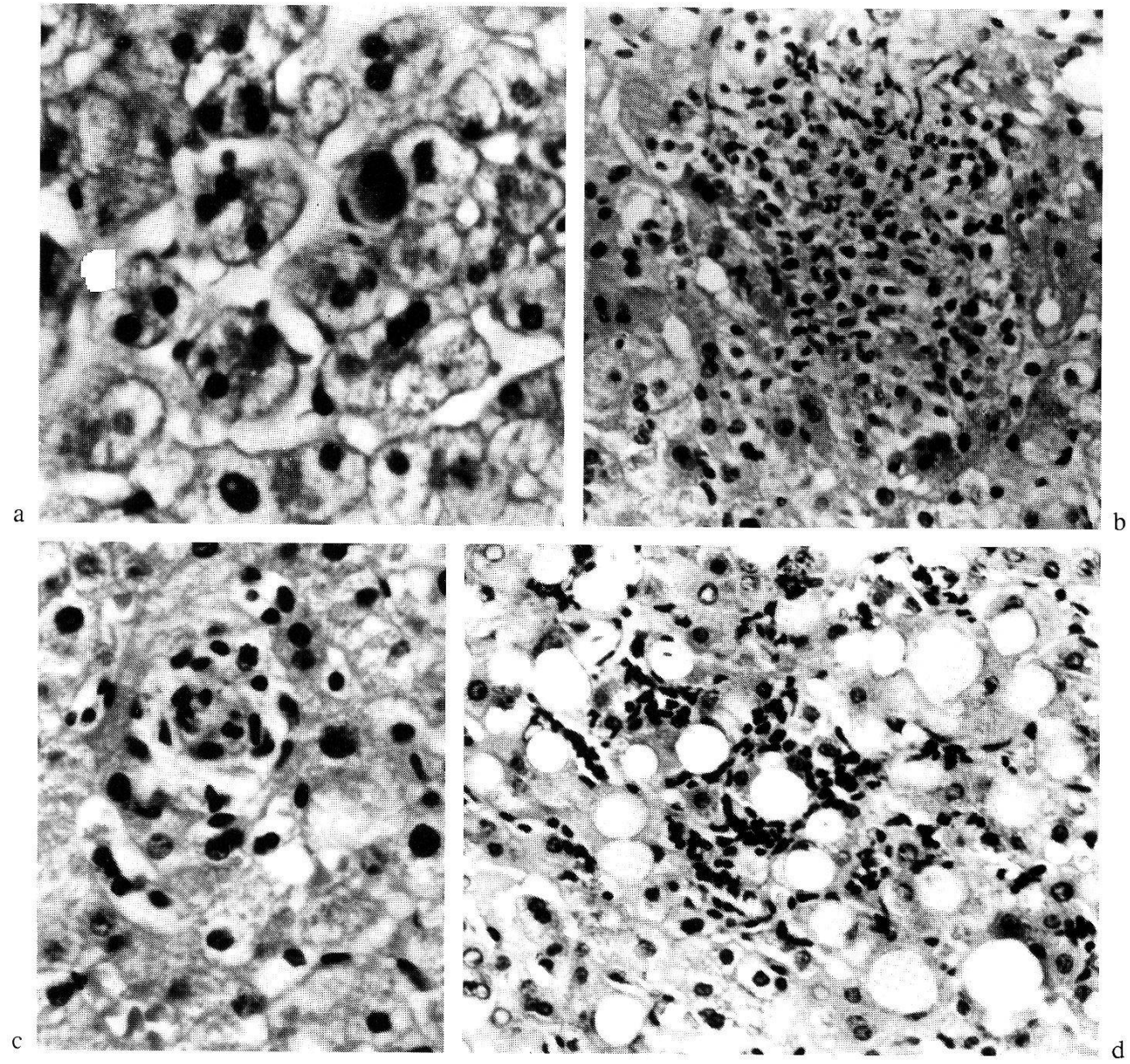

Fig. 1. All photomicrographs are of hematoxylin-eosin stained sections of liver biopsies. a) Acidophilic hepatocellular necrosis is present in the hepatic biopsy taken from patient 1 soon after the onset of fever, ×375; b) lobular foci of hepatocellular necrosis and leukocytic inflammatory infiltration from liver biopsy of patient 3 on day six of fever vary in size, ×240; c) lobular focus of hepatocellular necrosis and leukocytic inflammatory response in liver biopsy of patient 4 on day 13 of boutonneuse fever, ×375; d) multifocal mononuclear inflammation infiltrates hepatic lobule with moderate fatty change in liver biopsy from patient 7 thirty days after onset of boutonneuse fever, ×240.

granulomatous hepatitis of Q fever in which aggregates of macrophages form a peculiar doughnut arrangement (Picchi et al., 1960; Pellegrin et al., 1980). *C. burnetii* resides within the phagolysosome of macrophages, the target cell of Q fever (Burton et al., 1971), whereas, in most organs, endothelial cells are the target of *R. conorii* (Walker and Gear, 1985). The target cell of *R. conorii* in liver awaits further study of natural and experimental infection. In fatal cases of infections of *R. conorii* in South Africa, immunofluorescent rickettsiae were

observed in hepatic sinusoidal lining cells in two fatal infections (Walker and Gear, 1985). These foci of rickettsial infection had adjacent foci of necrosis, thus suggesting a role for rickettsiae in hepatocellular injury. Clearance of rickettsiae from lesions in the biopsy specimens of these non-fatal infections apparently is mediated by the influx of lymphocytes and macrophages.

These lesions resemble multifocal hepatocellular necrosis and inflammation observed in mice infected experimentally with *R. conorii* (Montenegro et al., 1984). The observations that similar lesions occur in both immunocompetent and T-lymphocyte deficient mice although more rickettsiae persist in the immunodeficient mice suggest that immunopathologic mechanisms are not important in the pathogenesis of these lesions. Likewise, the fatal infections reported from South Africa contained foci of necrotic hepatic cells that had provoked no inflammatory cell response. Future studies of human and experimental animal specimens by electron microscopy and immunohistochemistry will be important in characterizing of the populations of inflammatory cells and subpopulations of T-lymphocytes as well as identifying of the target cell in the liver.

Finally, our most important conclusion of this study is that boutonneuse fever is not benign with rare extracutaneous involvement. The hepatic lesions in seven consecutive patients although showing no clinical signs of hepatic disease reveal that *R. conorii* is frequently viscerotropic. The threat appears most severe for patients of older age, male sex, glucose-6-phosphate dehydrogenase deficiency, and alcohol abuse (Piras et al., 1983; Raoult et al., in press; Ruiz et al., 1985; Shulchynska, 1982).

Acknowledgments

The authors wish to thank Miss Lorraine Zeiler for assistance in preparation of the manuscript and Mrs. Barbara Hegarty for assistance in the preparation of the photomicrographs.

Burton P. R., Kordova N., Paretsky D.: Electron microscopic studies of the rickettsia *Coxiella burnetii:* entry, lysosomal response, and fate of rickettsial DNA in L-cells. Canad. J. Microbiol. *17*, 143–150 (1971).

Faure J., Escande J. C., Grataloup G., Massot C. H., Faure H.: Hépatite granulomateuse rickettsienne: intérêt de la biopsie hépatique. Nouv. Presse méd. *6*, 2896 (1977).

Gear H. H., Miller G. B., Martins H., Swanepoel R., Wolstenholme B., Coppin A.: Tick-bite fever in South Africa. The occurrence of severe cases on the Witwatersrand. S. Afr. med. J. *63*, 807–810 (1983).

Grillo-Reina A., Perez-Jimenez F., Escauriaza J., Jimenez-Alonso J., Molina-Padilla J., Jimenez-Preperez J. A.: Fiebre botonosa: estudio de los factores pronósticos. Rev. clín. esp. *166*, 51–53 (1982).

Guardia J., Martinez-Vazquez J. M., Moragas A., Rey C., Vilaseca J., Tornos J., Beltran M., Bacardi R.: The liver in boutonneuse fever. Gut *15*, 549–551 (1974).

Houvenaeghel M., Ottamani A., Raoult D., Rouzaud M., Manelli J. C., Bimar J.: Une forme grave de fièvre boutonneuse méditerranéenne. Ann. franç. Anesth. Réanim. *3*, 134–136 (1984).

La Rosa F., Sturniolo G., Caruso R., Ricciardi F., Ruggeri P.: Comportamento di OCT e SDH del siero in pazienti con febbre bottonosa. G. Mal. infett. parassit. *33*, 819 (1981).

La Rosa F., Ruggeri P., Sturniolo G., Calvo R.: Saggio di alcuni enzimi serici (MDH, LDH, ICH) in corso di febbre bottonosa. Acta medit. Patol. inf. trop. *1*, 419 (1982).

Moncharmont D., Miro I., Simonin R., De Micco C.: Hépatite granulomateuse à *Rickettsia conorii*. Nouv. Presse méd. *10*, 3651 (1981).

Montenegro M. R., Mansueto S., Hegarty B. C., Walker D. H.: The histology of "tache noire" of boutonneuse fever and demonstration of *Rickettsia conorii* in them by immunofluorescence. Virchows Arch. path. Anat. *400*, 309–317 (1983).

Montenegro M. R., Walker D. H., Hegarty B. C.: Infection of genetically immunodeficient mice with *Rickettsia conorii*. Acta virol. *28*, 508–514 (1984).

Morreale S., Mansueto S.: Studio di alcuni parametri enzimatici in corso di febbre bottonosa III – transaminasi (TGO-TGP) e fosfatasi alcalina. Acta medit. Patol. inf. trop. *2*, 133 (1983).

Pallot J. L., Voisin S., Cahuveau P., Fadel N., Kleinknecht D., Mariel C.: La forme maligne de la fièvre boutonneuse méditerranéenne. Presse méd. *13*, 1398 (1984).

Pellegrin M., Delsol G., Auvergnat J. C., Familiades J., Faure H., Guiu M., Voigt J. J.: Granulomatous hepatitis in Q fever. Hum. Path. *11*, 51–57 (1980).

Philip R. N., Casper E. A., Ormsbee R. A., Peacock M. G., Burgdorfer W.: Microimmunofluorescence test for the serological study of Rocky Mountain spotted fever and typhus. J. clin. Microbiol. *3*, 51–61 (1976).

Picchi J., Nelson A. R., Waller E. E., Razavi M., Clizer E. E.: Q fever associated with granulomatous hepatitis. Ann. intern. Med. *53*, 1065–1074 (1960).

Piras M. A., Calia G., Saba F., Gakis C., Andreoni G.: Glucose-6-phosphatase dehydrogenase deficiency in male patients with Mediterranean spotted fever in Sardinia. J. infect. Dis. *147*, 607–608 (1983).

Raoult D., Gallais H., Ottomani A., Resch J. P., Tichadou D., DeMicco Ph., Casanova P.: La forme maligne de la fièvre boutonneuse méditerranéenne. Six observations. Presse méd. *12*, 2375–2378 (1983).

Raoult D., Zuchelli P., Weiller P. J., Charrel C., San Marco J. L., Gallais H., Casanova P. (Manuscript accepted for publication).

Ruiz R., Martin A. M., Sanz F., Mateos A., Becares M., Querol R., Cunado A., Portugal J.: Complicaciones de la fiebre botonosa mediterránea. A propósito de dos observaciones. An. Med. intern. *1*, 32–36 (1983).

Ruiz R., Herrero J. I., Martin A. M., Sanz F., Mateos A., Hernandez A., Querol R., Portugal J.: Vascular permeability in boutonneuse fever. J. infect. Dis. *149*, 1036 (1984).

Ruiz R., Herrero J. I., Martin A. M., Vincent V. C., Sanz F., Mateos A., Querol R., Portugal J.: Formas graves de fiebre exantemática mediterránea. Análisis prospectivo de 71 enfermos. An. Med. intern. *2*, 365–368 (1985).

Shulchynska H.: Spotted fever in the Negev. Harefuah *102*, 317–319 (1982).

Staiti A.: L'interessamento epatico nella febbre bottonosa. Primi dati agobioptici. Acta medit. Patol. inf. trop. *1*, 393 (1982).

Walker D. H., Cain B. G.: A method for specific diagnosis of Rocky Mountain spotted fever on fixed, paraffin-embedded tissue by immunofluorescence. J. infect. Dis. *137*, 206–209 (1978).

Walker D. H., Gear J. H. S.: Correlation of the distribution of *Rickettsia conorii*, microscopic lesions, and clinical features in South African tick bite fever. Amer. J. trop. Med. Hyg. *34*, 361–371 (1985).