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By

L. D. Knyazeva and Ye. S. Yefimova

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CLINICAL COURSE AND CERTAIN PROBLEMS OF DIFFERENTIAL DIAGNOSIS OF Q FEVER

L. D. Knyazeva and Ye. S. Yefimova

Q fever was first detected in the USSR in 1950-1953 in Central Asia (I. A. Shifrin, M. P. Chumakov, A. P. Belyayeva, N. I. Khodukin, Ye. N. Bartoshevich, V. A. Lysunkova). It was soon found that epidemic reservoirs of this disease are present in many regions and republics of the country, especially where animal husbandry is developed. In recent years individual cases of outbreaks of the disease have been observed in large cities far removed from epidemic regions. In cities, mainly persons who come into contact in their work with hides or meat carcasses, with infected cotton, and more rarely those who use milk product brought in from epidemic areas were the ones who became ill with Q fever (M. P. Chumakov, Ye. V. Leshchinskaya, Ye. S. Ketiladze, V. A. Lashkevich).

According to the data in the literature, the clinical aspects of Q fever are diverse. The disease can occur as a type of grippelike, septic, pneumonic, nervous, or latent obliterated form (Meldolesi, Ye. V. Leshchinskaya, N. I. Levin, et al.), which is explained by the different modes of transmission of the infection.

We were interested in a description of the clinical demonstrations of sporadic cases of the disease whose diagnosis meets with the greatest difficulties. Sporadic infections of Q fever were annually manifested among persons who in the main arrived from epidemic foci or who worked in the textile industry. In certain cases, diagnosis of the disease met with difficulties and a differential diagnosis was made between influenza, typhoid fever, typhus, and even acute miliary tuberculosis.

In November 1959, three patients, students of the Institute of the Meat and Milk Industry, arrived at the Influenza Department of the hospital. Several patients were still in the ward where they were sent. The symptoms of the disease, an acute onset, chills, severe headache, malaise, slight rhinocleisis in one of them, and dry cough, made it possible to diagnose influenza in the patients. However, the further course of the disease, the more prolonged fever (6-7 days), sparse catarrhal phenomena, in spite of being the winter time, did not quite correspond to influenza. In two other students who arrived 3-4 days later with the same clinical symptoms, Q fever was first suspected when the epidemiologic data was taken into account, and then diagnosed as such.

We will cite a brief extract from a case history.

> Patient Z, age 21. Sixteen days before the disease was in the abattoir of the meat combine for several hours. Became acutely ill with chills on Nov. 17. Headaches, weakness immediately appeared and temperature rose to 38.5°. Nov. 18, temperature was 39.5°, chills again, severe headache. Nov. 19, condition not improved, the patient went to doctor and was hospitalized.
>
> On admission: condition severe. Temperature 40°. Severe headache, dizziness, rheumatic pains in small of back, in legs, anorexia, acute weakness as a consequence it was difficult to stand. General asthenia and dragginess were observed.

Mild episcleritis, hyperemia of face and fauces. Infrequent dry cough. Vesicular respiration heard in all divisions of lungs. Pulse lags behind temperature. Arterial pressure 120/80 mHg. Stomach soft, pain-free. Edge of the liver was identified 1 cm below the costal arc, spleen palpated in side position. Stool normal.

On the basis of the clinical course of the disease and the patients visit at the meat combine, a preliminary diagnosis of Q fever was established. Changes were not noted in lungs on roentgenoscopy of chest on 4th day of disease. Blood analysis: leucocytes 7900, plasma 24%, serum 23%, lymphocytes 44%, monocytes 9%; E.S.R., 4 mm per hour. Urine without pathological changes. Upon treatment with tetracycline, temperature dropped to normal on 6th day of illness, condition rapidly improved, however, weakness remained for a week.

On investigation of serum taken on 6th day of illness, a positive response in a titer of 1 : 40 was obtained in the complement fixation reaction with the antigen from Coxiella burneti. On 25th day of illness, complement fixation with blood serum was positive in a dilution of 1 : 160.

At this time the hospital had two other patients, workers of the meat combine, who were preliminarily diagnosed to have typhoid fever on the basis of the clinical picture and only on further examination was Q fever established.

During the last two months of 1959 and January 1960, Q fever was diagnosed in 27 patients and retrospectively established in 9 on the basis of the epidemiologic data and serologic examinations. Thus, 36 persons were under observation.

The group admission of patients was associated with an outbreak of Q fever at the meat combine, where animals were sent from various regions of the country. Of the 36 patients, 15 worked in the abattoir, dressing shop, and in the coolers of the meat combine. Among them were also machinists, plumbers, and mechanics who were not in direct contact with the animals, but frequently dropped in at the slaughterhouse. Another group of patients were 14 students of the Institute of

the Meat and Milk Industry who spent September through December at the meat combine doing practical work.

Of the remaining patients, one was a student of the Institute of the Meat and Milk Industry, another worked at the meat-canning plant, another patient had never been to the meat combine but his wife worked in one of the departments there. The cause for the possible infestation of four patients could not be established.

The diagnosis of Q fever was confirmed in 33 patients by the serologic data (increase in the titers of complement-fixing antibodies) and separation of Coxiella burneti from the blood of two patients. After the 12th day of the disease it was impossible to obtain blood serum from 3 patients.

Among those ill, 34 were men and 2 were women. A severe form of the disease was observed in 6 persons, average severity in 30.

The illness most frequently began acutely, from the demonstration of severe chills or mild, intermittent chills, headache, malaise, general jadedness, rise of temperature. In half the patients a high temperature was established from the first day of illness. In a third of the patients it reached the highest figures on the 3-5th day of the disease and held at that level for several days. The temperature can be graphically depicted first as a straight line denoting a constantly high temperature, then as a sloping hump with the apex on the 3-4th day of the disease for some patients with appreciable remissions during the day. Only 5 persons had a fever lasting 5 days. In others it lasted longer: 6 days in 8 patients, 7-8 days in 13, 9-11 days in 7 and more than 11 days in 3 persons. In the overwhelming majority of the patients the fever dropped lytically.

One of the main complaints of all those sick was cephalalgia, especially severe during the first days of the sickness. In 7 persons

it was accompanied by ophthalmalgia, in 29 by malaise. The frequency of individual symptoms in Q fever was as follows. Acute onset was observed in 33 persons. Thirty-six patients had cephalalgia, 34 had chills, 31 had diaphoresis, 28 suffered malaise, 7 were with ophthalmalgia, general astenia in 31, anorexia in 23, 2 had sore throats, 6 had epigastralgia, vomiting in 7, insomnia in 8, 10 had dizziness. Rigidity of the occipital muscles and Kernig's sign were noted in 4 patients, hyperemia of the face in 9, paleness in 11, episcleritis in 12, hyperemia of the fauces in 14, rhinocleisis in 6, dry cough in 19, thoracodynia in 2, dry rale in the lungs was noted in 15, focal pneumonia in 3, pulse lagging behind temperature in 28, tachycardia in 2, hepatomegaly in 21, and splenomegaly in 13 patients.

The chills observed in 34 persons at the onset of the disease were then repeated in half the cases over a course of 3-8 days, frequently being accompanied by profuse sweat. Both during a high temperature and after its normalization we noted general asthenia, which was quite evident in 9 persons. Dullness of the tones and the occurrence of a transient systolic murmur at the apex was detected with regard to the heart in 4 patients. The arterial pressure dropped moderately and only in 3 patients at the height of the fever was its maximal figures below 90 mHg.

As is known, due to the frequent affection of the lungs, Q fever is relegated to pneumorickettsioses. According to the data of certain authors, the per cent of pulmonary affections reaches 70-90.

Changes in the lungs are noted considerably more rarely by Soviet clinicians. S. A. Reynberg (10 out of 27), I. L. Kasatkina (in 22.6% of patients), and D. N. Ketiladze (16 out of 51) more often than others observed pneumonia in Q fever. Ye. V. Leshchinskaya found pulmonary infiltrates in 6.6% of the cases, Ye. N. Bartoshevich in 10-12%.

Ye. S. Ketiladze was not able to detect a single case of pneumonia in the outbreak at the carpet and suede combine.

The following changes were noted in the respiratory organs among the patients examined. Catarrhal phenomena of the upper respiratory tract were almost absent. Fifteen patients had a dry cough accompanied by dry rales in the lungs. The rales were heard either scattered throughout the lungs or localized in limited areas, most often in the lower lobes. Phenomena or bronchitis persisted several days and disappeared with a drop in temperature. In 3 patients the presence of crepitant rales made it possible to diagnose fine focal pneumonia which could not be detected in the roentgenoscopic examination. The patients generally noted a decrease or loss of appetite. Six persons complained of epigastralgia and pain in the right hypochondrium. The epigastral pains were somewhat enhanced on palpation.

Hepatomegaly and splenomegaly are characteristic for Q fever. The spleen was usually palpated from the 3-5th day of the disease in the side position for 2-6 days. The liver proved to be enlarged for 3-10 days up to the 6-15th day of the disease, and in individual patients protruded from under the rib margin by 2-4 cm, more often by 0.5-1.5 cm from the edge of the costal arc. The stool remained normal or was retained. Reaction of the kidneys was demonstrated by a slight albuminuria from 0.03 to 0.6%, microhematuria with the presence of fresh and lixiviated erythrocytes. Changes in the urine were very transient, usually detected in one analysis, with the exception of 2 patients in whom unaltered erythrocytes were detected up to the 6-12th day of the illness.

Changes of individual organs and systems were developed against a background of general intoxication, which was rather sharply expressed in 22 patients. In the other patients the sense of well-being

deteriorated little in spite of high temperature and headaches. The patients remained active, had almost no loss of appetite, read, walked about the ward, although general asthenia and jadedness was noted in them.

Torpidity and poor sleep were noted in patients on marked general intoxication. Indistinct meningeal phenomena were noted in 4 patients having a high temperature for 1-2 days. The cerebrospinal fluid investigated in one case remained normal. The condition of the patients improved with drop in temperature, but general asthenia persisted for 1 - 1 $^1/_2$ weeks.

We will cite as an example a brief extract from a case history.

> Patient T, age 22, splitter at the meat combine. Admitted to the department on Jan. 7, 1960, on the 5th day of illness, with complaints of severe cephalalgia, ophthamalgia, lumbar pains, pain in the upper half of the stomach, anorexia, asthenia. Acutely ill. Temperature increased immediately to 39°. During the following 4 days, temperature was 39-40°, severe cephalalgia, daily chills. Treated with headache pills.
>
> On admission: general condition was severe. Temperature 39.7°, evident intoxication. Patient sluggish, somewhat slowed. Expressed episcleritis, hyperemia of the face. Skin and fauces clear. No catarrhal phenomena. Vesicular respiration in lungs. Pulse appreciably lags behind temperature, dicrotic. Arterial pressure 90/60 mHg. Tongue dryish, brown coating. Sharp pain in epigastrium and hypochondria, enhanced on palpation. Liver and spleen not felt. Slight rigidity of occipital muscles. Blood analysis on 5th day of illness: leukocytes 11,400, plasma 58.5%, serum 21.5%, lymphocytes 18.5%, monocytes 1.5%; E.S.R. 6 mm per hour. Urine, 0.6% albumin, specific weight 1020, sporadic erythrocytes in preparation.
>
> Clinical diagnosis: Q fever.
>
> Temperature remained high until the 8th day of illness. It was possible to palpate the liver on the 7-8th day of illness upon a decrease of abdominal pains. Cephalalgia and rheumatic pains disappeared with an abatement of temperature, but rather severe weakness persisted on discharge.

Blood analysis on 10th day of disease: leukocytes 5700, plasma 4%, serum 40%, lymphocytes 48%, monocytes 8%; E.S.R. 15 mm per hour. Complement fixation with blood serum taken on 6th and 11th day of illness, negative with antigen of Q fever. Complement fixation was positive in a titer of 1 : 640 on 50th day of sickness.

In this case the diagnosis of Q fever did not cause doubt when the patient entered and it was later confirmed in the laboratory.

The degree of evidence of general intoxication can also be judged by the sharp shift of the blood formula to the left, up to 53.5% stab-nuclear forms. Moderate leukocytosis was noted only in 5 persons. The number of leukocytes usually remained normal or slightly decreased (7 persons) during the course of the disease. The degree of leukopenia did not depend on the severity of illness. The E.S.R. as a rule remained normal, but in 5 patients varied within 15-25 mm per hour. The greatest changes were noted in the blood formula (sharp shift to the left). In 22 patients the per cent of stab-nuclear forms was more then 15. The blood rapidly normalized with the disappearance of intoxication. The illness in all patients ended with recovery, but in 3 of them second febrile waves were noted. Relapses developed on the 2nd, 4th, and 5th day after the temperature returned to normal. Fine focal pneumonia was detected in one patient during the second wave. Widal's reaction, complement fixation with the antigen of Rickettsia prowazekii, performed on 26 patients, remained negative. Negative results were also obtained on examination of fresh serum of 5 patients in relation to leptospiral jaundice and leptospirosis grippothyphosa (swamp fever).

As was already noted above, all patients were admitted with the diagnosis of influenza. An erroneous diagnosis of influenza was also made in the department on 6 patients with Q fever since the clinical features had great similarity with influenza and the epidemiological anamnesis was not immediately taken into account.

For an example we will cite a short extract from a case history.

> Female patient Sh, age 21, student at the Institute of the Meat and Milk Industry. Admitted to the department on Nov. 29, on second day of illness, with complaints of cephalalgia and asthenia. Became acutely ill, temperature rose to 39°, headache and slight malaise demonstrated.
>
> On admittance: condition, average severity. Temperature 38.2°. Face, normal. Fauces, sclera, skin clear. Pulse lags behind temperature. Arterial pressure 100/60 mHg. High temperature maintained for next 3 days, caphalalgia, profuse sweating noted. Liver and spleen not felt. Temperature normal from Dec. 3.
>
> Blood analysis on 2nd day of illness: leukocytes 4200, plasma 32%, serum 43%, lymphocytes 14%, monocytes 10%; E. S. R. 5mm/hr. Urine: 0.06% albumin, sporadic lixivated and unaltered erythrocytes in preparation.
>
> Clinical diagnosis: influenza.
>
> However, the presence of five-day fever, the absence of catarrhal phenomena with respect to the nasopharynx, the epidemiological data, compelled examination for Q fever. On the 10th day of the disease the complement-fixation test was positive in a titer of 1 : 640. The strain Coxiella burneti was separated from blood sampled on the 4th day of illness at a temperature of 39°.

In this case, as in 5 other patients in whom influenza had been diagnosed, catarrhal phenomena from the side of the nasopharynx, characteristic for influenza, were absent, persistant bradycardia, recurrent chills, sweats, and hepatomegaly were noted. A fever lasting 6-8 days, observed in these patients, is rarely encountered in influenza, especially during the interepidemic period.

In addition, in simple influenza intoxication lasts 1-2, rarely 3 days even in those cases when the febrile period is somewhat prolonged. Here symptoms of intoxication were still evident on the 4-6th day of illness. The epidemiologic anamnesis is without doubt important in diagnosing Q fever.

Symptoms characteristic of influenza, typhoid fever, and thyphus were diversely combined in the clinical picture of the observed patients. This is why the other group of patients were originally diagnosed erroneously to have typhoid fever.

We will cite a brief extract from a case history.

> Patient C, age 35, mechanic of the meat combine. Passed through the abattoir daily. Admitted Nov. 3, on 5th day of illness, with complaints of cephalalgia, malaise, poor sleep, anorexia, general asthenia.
>
> Became acutely ill when he felt chills and headache. Temperature immediately rose to 39° during the days before admittance to the hospital. The patient had chills and profuse sweat daily, troubled by severe headache.
>
> On admittance: condition, average severity. Temperature 40°. Pale. Skin clear, moist from sweat. Mile rhinocleisis, infrequent dry cough. Scattered dry rales heard in the lungs. Pulse almost corresponds to temperature. Arterial pressure 100/60 mHg. Tongue moist, white-coated. Abdomen soft, not distended. Liver protrudes from under the costal arc by 3 cm, spleen palpated in side position. Patient suffers with insomnia.
>
> Blood analysis on Nov. 3: leucocytes 5200, plasma 16%, serum 40%, lymphocytes 4%; E.S.R. 24mm/hr.
>
> On the basis of the prolonged fever, cephalalgia, paleness, hepatomegaly and splenomegaly, and blood picture, typhoid fever was diagnosed, and on Nov. 5 treatment with levomycetin, 3 g per day, began.
>
> Subsequently, in spite of the use of levomycetin, a high temperature, headache, recurrent chills, sweating, and general asthenia were noted.
>
> All laboratory investigations relative to typhoid fever invariably yielded negative results.
>
> The complement-fixation reaction with the antigen of Q fever on the 28th day of the disease was positive in a titer of 1 : 2560, but on investigation on the 15th day it had been negative.

In the clinical picture of this patient, as in the other two, the presence of prolonged fever, general intoxication, headaches, poor

sleep, decrease of appetite, bradycardia, facial pallor, enlargement of the liver and spleen created the similarity with typhoid fever.

However, in spite of the high, prolonged fever, there was no characteristic typhoid state, profuse sweats and frequent chills had been noted, and there was no therapeutic effect from levomycetin. The negative laboratory data also did not make it possible to stop on a diagnosis of typhoid.

There were still great diagnostic difficulties in those cases where the patients arrived from different places and there was no possibility to establish the cause of the affection. There were 7 such patients. Although on the basis of the clinical picture Q fever was suspected in 3 patients by eliminating other diseases, the diagnosis was established only after laboratory confirmation when the patients already had a normal temperature. Either influenza with pneumonia or typhoid and typhus were originally proposed for 4 patients. In spite of the similarity with typhus, especially at the onset of the disease as a result of cephalgia, sleeplessness, hyperemia of the face, scleritis in two of them, and an 8- to 10-day fever, it was not possible to detect typhus upon careful examination. There was no characteristic euphoria, the pulse appreciably lagged behind the temperature, and profuse sweating and chills were noted. The complement-fixation reaction with Rickettsia prowazekii remained negative.

On analysis of the serologic data for Q fever it was found that fixation of the complement in diagnostic titers (1 : 40, 1 : 80) is rarely positive on the 5-9th day of the disease. During this period the reaction was positive in 3 of the 15 examined (in those whose fever did not last more than 5-6 days). In 11 of 22 examined patients with Q fever, the complement-fixation reaction was positive at the end of the 2nd week. Negative responses were in those who still had

a temperature, or the temperature had just dropped, or the patients had received much biomycin or levomycenin. At the 3rd week of the disease, 2/3 of the patients and all 14 of those investigated at later dates had a positive complement-fixation reaction. In patients of the control group (pneumonia, influenza) the reaction was negative or positive in a titer of 1 : 5 or 1 : 10.

Titers of 1 : 320 and higher, up to 1 : 2560, rarely 1 : 160 and 1 : 80 were usually observed in Q fever.

The clinical diagnosis of Q fever in the observed patients was facilitated by the presence of an outbreak. In the majority of patients, diagnosis was established in the acute period of the disease during an outbreak and not after its end as is frequently observed.

However, diagnosis of sporadic cases is possible by taking into account the epidemiologic data. We must bear in mind the probability of Q fever in patients with a 5- to 9-day fever with severe headaches, chills and sweats, symptoms of general intoxication, phenomena of mild bronchitis, hepatomegaly, splenomegaly, abrupt neutrophil shift in the blood formula, a positive serologic investigation, and consideration of their occupation and other epidemiologic data.

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