J. health med. sci.,
8(3):173-184, 2022.

Update on the diagnosis, management and treatment of fever of unknown origin: review article and case report

Actualización en el diagnóstico, manejo y tratamiento de la fiebre de origen desconocido: artículo de revisión y reporte de caso

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DELGADO, J.; GÓMEZ, G.; ARANEDA, O., TAUREAUX, N.; PANDOLFI, M.; SOTO-SUAZO, M. Update on the diagnosis, management and treatment of fever of unknown origin: review article and case report. *J. health med. sci., 8(3)*:173-184, 2022.

ABSTRACT: Introduction: Actually, there are more than 200 different causes of unknown fever, it is necessary for the doctor to identify the most prevalent causes of unknown fever in our Clinical boar. **Presentation:** A 52-year-old male patient with no history of chronic diseases, which was received in the Emergency Service of the Hospital San Pablo, Coquimbo, on 02/03/20 began a clinical picture characterized by fever up to 39 ºC associated with diaphoresis, evaluated several times in primary health care without response to symptomatic treatment. He denies dyspnea, cough, sputum production, headache, muscle weakness, myalgia, fainting, decreased visual acuity, nausea, vomiting, chest pain, abdominal pain, diarrhea, constipation, altered bowel movements, weight loss, dysuria, bladder tenesmus, pain lumbar, skin lesions. As relevant information, the patient reports having taken amoxicillin/clavulanate for 2 days on his own account. **Discussion:** Physicians should be aware of the rare extent of an unusual presentation of knowledge origin fever, probably associated with Still disease, as well as medical options for treatment. The literature does not conclude on a gold standard for the method of approach. **Conclusion:** In our case, the etiological agent that could cause Fever of unknown origin (FUO) was Sars cov-2 given the presence of elevated inflammatory factors and acute phase proteins and the presence of neutrophilic infiltration.

KEYWORDS: FUO, infection disease, autoimmune disease, sarscov-2& Still disease.

INTRODUCTION

"Since the origins of medicine, fever has been one of the basic alterations of bodily normality that has led the affected person to seek help. (Hippocrates, 4th century B.C.). Within the signology and accompanying symptoms of fever, we find pain, functional impotence and bodily deformity", also known as the Celsus tetrad (Quinto Aulio Celsus, IV century A.C.). Normal body temperature is maintained within a narrow intra-individual and somewhat wider inter-individual range, independent of environmental variations and body coverage (Barnard, 19th century A.C.).

We understand Fever of Unknown Origin (FUO) as the presence of a body temperature above 38.3 ºC, for a period of not less than three weeks, a definition proposed by Petersdorf and Beeson (1961) as: 1) a temperature greater than 38.3 ºC measured on several occasions, 2) with a duration of more than three weeks and 3) in which a diagnosis is not reached despite a one-week study with the hospitalized patient. Although this classification has persisted for more than 30 years, with no history of hospital stay, neutropenia or human immunodeficiency virus (HIV) infection persists undiagnosed despite adequate studies and after at least three outpatient visits or three days of hospital stay. Durack and Street have proposed a revised system for FUO classification that takes more into account non-endemic and emerging diseases, better diagnostic technologies, and adverse reactions to new therapeutic interventions (Fuentes *et al.*, 2018).

This pathology constitutes one of the greatest diagnostic challenges for the clinician and the internist given that there is a high rate of inaccuracies

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in the diagnosis, which leads to classifying it from the etiological point of view as idiopathic, corresponding to 30% of the cases, not finding apparent cause.

In order to avoid losing information, we must investigate and be a kind of private investigator or detective where we must carry out a through anamnesis, asking directly about travel, contacts, animal and insect exposure, medications, immunizations, family history, heart valve disease, previous treatments or surgeries, especially, if they are cancer patients and because of the type of medication they are using, their sexual and hygienic habits; All this focused on the history and the patient's account, performing a complete physical examination and complementing it with imaging tests and laboratory tests.

In this narrative review and case report we have proposed to investigate the different clinical presentations and differential diagnoses that explain FUO, which has multiple focus and etiologies, constituting a real challenge to elucidate the origin or focus that explains the fever; which will be evident when examining the patient of this report (Rodríguez *et al.*, 2018).

Infectious causes correspond to the most frequent etiology of fever of unknown origin, within this tuberculosis is the most frequent cause (12-18%) in South America, whose systemic manifestations range from pulmonary to extrapulmonary, being the most frequent extrapulmonary.

Acronymus: HIV: Human immunodeficiency virus; HAS: healthcare-associated infections; CMV: cytomegalovirus; IRIS: Immune reconstitution inflammatory syndrome; CMT: Chemotherapy; IBD: inflammatory bowel disease. Own elaboration.

Table 1. Classification of Fever of Unknown Origin (FUO) according to clinical presentation, Durak and Street (1991).

Indicators	Classic FUO > 38ºC, >3 days, not present or incubating on admission	Nosocomial (FUO)	Immunosuppressive FUO	FUO in AIDS
Definition	>38 ºC >3 weeks >2 visits or 3 hospital days.	>38 ºC, >3 days, not present or incubating on admission.	>38 ºC, >3 days, cultures negative after 48 hrs>38 ºC >3 weeks >2 visits or 3 days in hospital.	>38 ºC, >3 weeks outpatient, >3 days in hospital. HIV Serology (+).
Patient location	Community, clinic, hospital.	Inpatient Hospital or clinic.	Hospital or Clinic.	Community, clinic, Hospital.
Cause	Neoplasms, infections, inflammatory states, hyperthermia, idiopathic.	HAS infections, post-operative complications, medication´s fever.	Mostly due to infections, documented cause in only 40-60%.	HIV primary infection, typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, IRIS.
Emphasis on history	Travel, contacts, animal and insect exposure, medications, immunizations, family history, heart valve disease.	Operations and procedures, devices, anatomical considerations, drug treatment.	CMT, administered medications, background immunosuppressive disorders such as bone marrow transplants and therapies with high myelotoxicity.	Drugs, risk factor exposure, travel, contacts, HIV stage.
Emphasis on Physical Examination	Oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum, or prostate, IBD.	Wounds, drains, devices, sinuses, urine.	Skin, IV sites, lungs, perianal area	Mouth, paranasal sinuses, skin, lymph nodes, eyes, lungs, perianal area.
Paraclinical or complementary tests	Hemogram, lymphocyte count, serology, chest X-ray, lung or bone marrow biopsies, culture and cytology for liver.	Images, cultures.	X-rays and CT imaging and cultures.	Hemogram, lymphocyte count, serology, chest X-ray, lung or bone marrow biopsies, liver for culture and cytology.

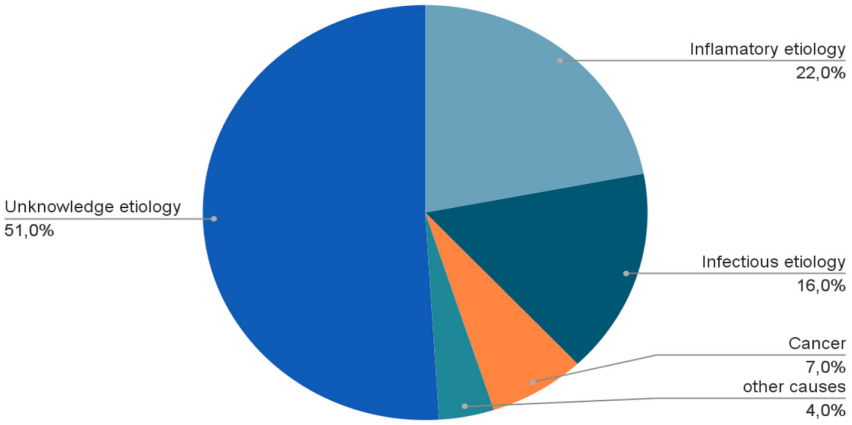

Figure 1. Etiologies of fever of unknown origin and its frequency (in percentage). Own elaboration. (Oncohema, 2018).

METHODOLOGY

Our protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMAP-Narrative Review), which was revised by the research team and members. The final protocol was registered prospectively with the Open Science Framework on 6 September 2016 (https://osf.io/kv9hu/)."

With the "Fever of unknown origin" AND "adult" strategy in the Epistemonikos platform and counting the results of the last five years, six systematic reviews were identified, 19 primary studies.

With the "Fever of unknown origin" AND "adult" strategy in the PUBMED platform, 35 results, of which 6 are systematic reviews, six correspond to clinical trials, two randomized clinical trials, 22 are literary reviews and three meta-analyses, and four were found duplicates.

With the search strategy "Fever of unknown origin" AND "adult" it was searched on the LILACS platform 33 results in total, 22 case reports, two control trials, two incidence´s studies, two screening studies, one diagnostic study, one clinical guide, one prevalence study, one prognosis study, one risk study. If the filter of the last five years is applied, they are reduced to eight, which comprise eight case reports, one diagnostic study, one screening study, of which two were repeated.

With the search strategy "Fever of unknown origin" AND "adult" it was searched in the EBSCO platform, Google Scholar, we found 739 results review articles, last 5 years. AND adult AND etiologies AND therapies AND diagnosis "Fever of unknown origin" Articles in English - Spanish, the years 2017-2022.

Subsequently, they were reviewed by two reviewers who read and analyzed each of the writings in parallel, eliminating and discarding those with incomplete data, gray literature and repeated articles using the epistemonikos platform at the time of performing the review matrix, selecting 24 primary studies.

PRESENTATION OF THE CLINICAL CASE

A 52-year-old male patient with no history of chronic diseases, on 02/03/20 began a clinical picture characterized by fever up to 39°C associated with diaphoresis, evaluated several times in primary health care without response to symptomatic treatment. He denies dyspnea, cough, expectoration, headache, muscle weakness, myalgia, fainting, decreased visual acuity, nausea, vomiting, chest pain, abdominal pain, diarrhea, constipation, altered bowel movements, weight loss, dysuria, bladder tenesmus, pain lumbar, skin lesions. As relevant information, the patient reports having taken amoxicillin/clavulanate for 2 days on his own account.

He refers not to use barrier contraceptive methods with a single sexual partner. Due to the foregoing, plus the persistence of the fever, he was referred on 02/06 to the emergency room of the San Pablo de Coquimbo Hospital, alert, attentive, in good

general condition, normal cardiopulmonary examination, abdomen without lesions, without adenopathy; admission to the medical service is decided, during the night of 02/06 he begins to present pustular exanthema in the first instance only in lower legs and the next day it appears in the chest, superior limbs, some of them with pus, not pruritic, this picture is It was accompanied by synovitis of both ankles, and also of some metacarpophalangeal joints of both hands. Rest of physical examination without alterations. In the emergency room, a chest X-ray was taken, which showed a slight bilateral perihilar thickening without evident pathological opacities or clouding of diaphragmatic recesses.

Laboratory tests: C-reactive protein (CRP) 171 UI/dL, lactate dehydrogenase (LDH) 351UI/Dl and leukocytosis. It is decided to enter the medical service with a diagnosis of febrile syndrome with unknown focus for study and management.

Patients admitted in regular general conditions for study of febrile syndrome. Laboratory tests are requested, where there is evidence of an increase in the inflammatory parameters CRP 172 UI/Dl on 02/07/20. Therefore, blood cultures were taken, which were negative, and antibiotic treatment was started with ceftriaxone 1 g every 12 hours. The patient persists with fever, with an increase in CRP reaching 430UI/Dl on 02/12/20, so in addition to ceftriaxone, cloxacillin 2 grams every 4 hours is started, which lowers the inflammatory parameters, reaching a CRP of 141 UI/Dl. laboratory tests: HIV, Hepatitis B virus (HBV), hepatitis C virus (HCV), Venereal Disease Research Laboratory (VDRL), Kinetics iron (high ferritin, low iron and transferrin), echocardiogram, Human leukocyte antigen B27 (HLA B27), and radiography of the hands, feet and ankles, to discover an infectious focus, without pathological findings.

A consultation with Dermatology was made, who performed a skin biopsy that reported neutrophilic folliculitis. In addition, culture of the pustular lesions was done, reporting positive for Staphylococcus epidermidis and hominis, concluding contamination of the sample. CRP for gonococcus and standard

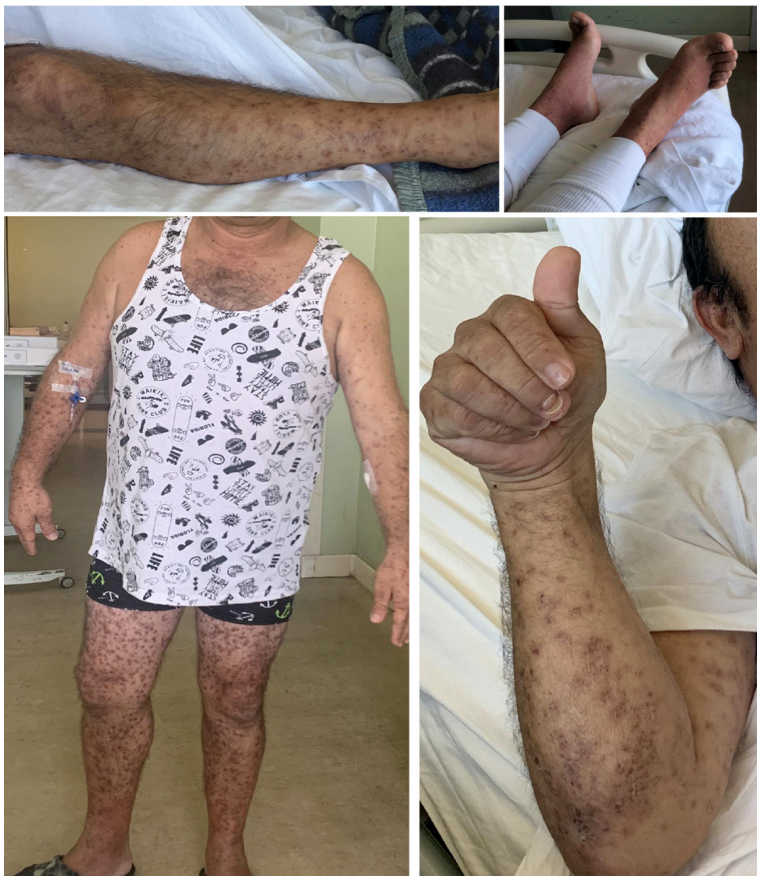

Figure 2. Erythematous skin lesions in the patient.

panel is also performed, all being negative. Regarding the rheumatology area, antineutrophil cytoplasmic antibodies (ANCA), extractable nuclear antigens (ENA), antinuclear antibody (ANA), ANTI-DNA were requested, resulting in negative and elevated complements (C3, and C4 45).

Echocardiogram performed on 02/12/20 does not show pathological findings, revealing the absence of images suggestive of vegetations. Finally, testicular echotomography was requested, since the patient reported long-standing pain in the right testicle, reporting cysts in the epididymis. A computes tomography (CT) scan of the abdomen and pelvis with contrast is also performed, which reports a focal segmental hepatic lesion suggestive of hemangioma and reveals retroperitoneal adenopathies. However, the radiologist suggests that a nuclear magnetic resonance (MRI) is necessary to better define the lesion, for which the request is made on day 06/03/20, pending completion date. Latest tests: Protein electrophoresis reporting hypoalbuminemia and mild hypergammaglobulinemia. On 02/26/20, an endoscopy order was performed, which was performed on 03/05/20 with no pathological findings.

Patient persists feverish throughout her hospital stay, on 03/04/20 last day of antibiotic treatment, patient remained afebrile for 24 hours, however, at 19 hours she presents another febrile episode of 37.6 ºC. Currently in good general condition, but without persistence of fever, for which it is decided to discharge him from hospital, remaining in an outpatient study, with an MRI time pending.

REVIEW BY SYSTEMS

1. **Infectious:** Admission in the context of sepsis without focus. Which study was performed: smear microscopy (02/07), complete urine (02/06), urine culture (02/06) and blood cultures (02/07), VDRL and treponemal tests which were negative. HIV Elisa test 07/02 (negative) was made. Antibiotic treatment was started with ceftriaxone at a dose of 1 gram every 12 hours IV. Procalcitonin with a value of 2.06 was requested. During hospitalization, the patient persists with fever, and elevation of inflammatory parameters, increased CRP (171→ 430) and white blood cell count (14,200→ 17,300 with predominance of segmented ones). Due to pustular lesions, antibiotic treatment with Cloxacillin 2 was started on 02/12 grams every 4 hours, with regular clinical response. A new blood culture was requested on 02/12 (negative). Procalcitonin from 02/13 at 1.43. On 02/15, patient with increased pustular lesions, for which contact isolation was performed. Currently lesions in remission, with completion of antibiotic therapy, completed 26 days with Ceftriaxone and 21 days with Cloxacillin; the fever persists yet. On 02/25/20, a CT scan of the abdomen and pelvis reported segmental focal liver injury, suggestive of hemangioma, in addition to retroperitoneal adenopathies, so on 03/06/20 an MRI of the abdomen and pelvis with triphasic contrast was requested.
2. **Dermatological:** On 02/10 he was evaluated by Dermatology. Dermatologist took biopsy and culture of pustules reporting neutrophilic folliculitis; positive culture for Staphylococcus epidermidis and hominis, concluding as contamination of the sample. Antibiotic treatment was continued due to suspicious of disseminated gonococcal infection versus reactive arthritis. Pustules persist, despite antibiotic treatment. CRP for gonococcus was performed, which was negative. Currently pustules are in remission with persistent fever.
   Culture of the pustular lesions, were reporting positive for Staphylococcus epidermidis and hominis, concluding contamination of the sample. CRP for gonococcus and standard panel was also performed, all being negative. Regarding the rheumatology area, ANCA, ENA, ANA, ANTI-DNA were requested, resulting in negative AND elevated complements (C3 and C4 C5).
3. **Cardiology:** Under diagnosis of febrile syndrome under study, on 02/12 a transthoracic echocardiogram was performed, which concluded normal cardiac cavities, absence of images suggestive of vegetations.
4. **Rheumatology:** Given symptoms of arthralgia with generalized pustules suspected of reactive arthritis, rheumatology evaluation was requested. Rheumatologist evaluated a patient who, under suspicion of reactive arthritis, starts with Celecoxib at 200 mg daily and requests HLA-B27 with a result (-) and hands and ankles´s X-rays, which showed no pathological findings. In addition, ANA, ENA,

ANTI-DNA, ANCA were requested, which were negative, and elevated Complements (C3 219 and C4 45). Protein electrophoresis was performed, highlighting hypoalbuminemia with mild hypergammaglobulinemia.

5. **Digestive:** due to a CT scan performed on 02/25/20 that reports abdominopelvic lymphadenopathies, upper and lower digestive endoscopy were requested (the colonoscopy was pending). Upper gastrointestinal endoscopy without pathological findings. In addition, carcinoembryonic antigen was requested, which was less than 0.5 µg/L.
6. Endocrine: Abdominal and pelvic CT scan with contrast on 02/25/20 reported a right thyroid nodule, so a thyroid echotomography was performed, which reported a diffuse goiter.
7. **Urological:** Patient referred right testicular pain during hospitalization, for which a testicular ecotomography was requested, which revealed cysts in the epididymis. In addition, prostate antigen was requested, which resulted in 0.52 ng/ml, and alpha fetoprotein of 1.6 ug/dL.
8. **Hematology:** Interconsultation with La Serena Hematology for suspicious of Lymphoproliferative Syndrome, in which no major findings were found.

DISCUSSION

Currently, cases of fever of unknown origin constitute a major challenge for both the general practitioner and the internist in their initial confrontation, one of its main causes being infectious origin, such as tuberculosis, intra-abdominal infections, subacute bacterial endocarditis (EBSA), Viral, Osteomyelitis, inflammatory or neoplastic origin, such as Non-Hodgkin Lymphomas (NHL), Leukemia, Renal Cell Carcinoma (RCC), Hepatocarcinome (HCC), liver metastases and colon cancer.

On the other hand, we find inflammatory autoimmune causes such as Still's disease, rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, dermatomyositis, scleroderma, complement diseases, temporal artery arteritis, and vasculitis.

1. Infectious Sphere

In the present case, according to the antecedents previously exposed; In relation to age and sex and by probability, an attempt was made to rule out in the first instance the causes of infectious origin, taking as a diagnostic hypothesis a disseminated gonococcal infection vs. Reactive Arthritis.

a) **Gonorrhea:** Gonorrhea is an STI caused by Neisseria gonorrhoeae. It is a common cause of urethritis in men and cervicitis in women. Although genital and extragenital gonorrhea can be asymptomatic, proctitis can occur, making the infection indistinguishable from other STIs. Disseminated gonococcal infection is reported in 1% to 3% of patients with gonorrhea. Case series highlight two different forms of disseminated gonococcal infection: purulent monoarthritis or oligoarthritis and a syndrome of dermatitis, tenosynovitis and migratory polyarthralgias, but the clinical spectrum is heterogeneous. Cutaneous findings are reported in 50% to 75% of patients with bacteremia. The skin lesions may resemble maculopapular and pustular lesions, like those seen in this patient. However, our patient, despite not using barrier methods as he had only one sexual partner, did not present positive tests for the presence of gonorrhea in serology, and no concomitant STDs at the time of taking the tests.

b) **Syphilis:** Syphilis is an infection caused by the spirochete Treponema pallidum and has been called the great simulator due to its multiple clinical presentations and its ability to manifest from sexually transmitted and dermatological diseases to even autoimmune and rheumatological diseases. The average incubation period is 2 to 3 weeks, although symptoms have been reported as early as 3 days after exposure. The primary lesion, or chancre, is usually an ulcer measuring 1 to 2 cm in diameter with an indurated margin. Penile injuries are common; perianal lesions may also be seen. Chancres are usually painless but can be associated with pain in some cases. The presence of multiple chancres is rare. The secondary stage of syphilis, known as secondary syphilis, is associated with systemic symptoms and lymphadenopathy (which is usually more generalized than the lymphadenopathy seen in this patient), as well as rash and a positive rapid plasma reagin (RPR) test. The patient in our case presented localized adenopathies accompanied by arthralgia and a maculopustular exanthema that spread throughout the

body and did not converge, but without positive treponemal and non-treponemal tests. (Laguado *et al.*, 2021).

c) **Sars Cov-2 Dermatology Manifestation:** Sars- Cov-2 is a positive single-stranded RNA virus, classified as a respiratory pneumonia, characterized by a cytokine storm and causes vascular damage such as the blood vessels of the body's banking organs, but also presents multiple skin manifestations which were described in various clinical series (Casas, et al, 2020). The group studied skin lesions in 375 COVID-19 patients included in a massive prospective survey, grouping these heterogeneous skin manifestations into 5 major clinical patterns. In a Spanish cohort of 666 cases hospitalized for COVID-19, found that 45% (304/682) of patients with mild to moderate COVID-19 had mucocutaneous findings (Nuno-González *et al.*, 2021). The mean age of the patients was 55.7 years, and most of them were women (58%) (Cozzi *et al.*, 2016). In a recent multicenter study, clinical data from 200 patients with skin manifestations associated with COVID-19 collected from 21 Dermatology Units in Italy were analyzed (Nuno-González *et al.*, 2021). Of the 200

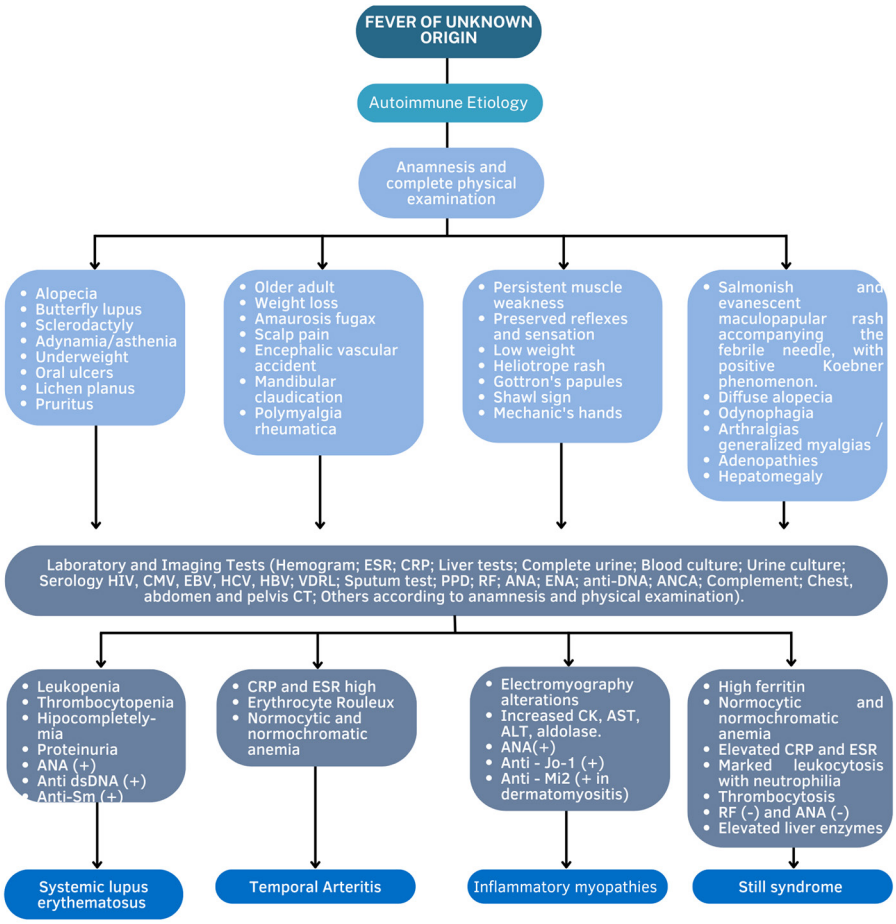

Figure 3. Outline of the management of fever of unknown origin of infectious etiology. Acronymus: ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HIV: Human immunodeficiency virus; CMV: cytomegalovirus; EBV: Epstein Barr virus; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; VDRL: Venereal Disease Research Laboratory; PPD: Purified protein derivative test; RF: Rheumatoid factor; ANA: antinuclear antibody; ENA: extractable nuclear antigens; ANCA: antineutrophil cytoplasmic antibodies; CT: computed tomography; Anti-Sm: Anti-Smith antibodies; CK: Creatinine kinase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase. Own elaboration.

patients with skin manifestations related to COVID-19, 54% were men, and their mean age was 57 years at the time of disease diagnosis (Marzano *et al.*, 2021).

From these series it was possible to classify skin phenotypes into 5 which are: Acral or acro-ischemic lesions Vesicular or varicelliform lesions Urticarial rash Maculopapular exanthema Livedoid or necrotic lesions. In the present case, pustular, urticarial, and maculopapular lesions with neutrophilic infiltration were found, which is consistent with what was shown in a Spanish series, given the patient's age of 52 years, which compromise the trunk, abdomen, flanks, groin and in a case the palms, and characterized histopathologically as vacuolar interface dermatitis, necrotic keratinocytes as well as mixed small-vessel vasculitis or with predominance of neutrophils. Some cases with lymphocytic exocytosis and foci of parakeratosis. (Rodríguez-Jiménez *et al.*, 2020 & de Perosanz-Lobo *et al.*, 2020)

2. Autoimmune Sphere

a) **Still's disease:** Directed questioning revealed pustular exanthema in the first instance only in lower legs and the next day it appeared in the chest, superior limbs, some of them with pus, not pruritic, this condition was accompanied by synovitis of both ankles, and also of some metacarpophalangeal joints of both hands, which is consistent with clinical signs compatible with Still's syndrome, given the dual pattern of fever, the presence of a rash on the trunk and extremities, arthralgia, conjunctival effusion, with diagnostic images showing retroperitoneal lymphadenopathies without splenomegaly and the presence of a hepatic hemangioma. He also presented laboratory markers with elevated ferritin and decreased transferrin, leukocytosis without initial elevation of alkaline phosphatase and with elevation to 171 mg/dl of CRP A 470 mg/dl during the course of treatment with ceftriaxone antibiotics. The type of exanthema that the patient presented was different from the present maculopapular and evanescent exanthema, with a positive Koebner, which was maculopapular that did not converge, so this differential diagnosis was ruled out (Yamamoto, 2012; Kikuchi *et al.*, 2014; Cozzi *et al.*, 2016).

b) **Lupus:** Systemic lupus erythematosus (latin, lupus = wolf) is an autoimmune-type disease that affects connective tissue and has wide range of clinical manifestations, among which at the beginning polyarthritis, ulcers mucocutaneous and malar erythema; systemic lupus erythematosus is one of the causes Non-infectious inflammatory diseases of fever of unknowledge origin. One of the diagnostic hypotheses that was tried to rule out was lupus, given the non-specific clinical presentation, which although it did not meet the age of classic presentation, an important cause of fever of unknown origin is this disease, which is very prevalent in this country, although it affects more young women than men. The patient presented a non-confluent maculopapular rash, without lupus butterfly and malar erythema. He presented arthralgias without elevation of ANA, ENA, RO, LA, SCL 70, anti double-stranded DNA antibodies. He also did not manifest adynamia and asthenia previously and within the personal history a history of rheumatoid arthritis, systemic lupus erythematosus, scleroderma or dermatomyositis was ruled out. An evaluation of the autoimmune markers was performed on a temporary basis, which was negative one year after the condition (Ribero *et al.*, 2017; Lenormand & Lipsker, 2021).

c) **Rheumatoid arthritis (RA):** RA is a disease with systemic compromise that usually presents: 1. Joint compromise, characterized by synovitis and joint destruction; and 2. Extra-articular involvement, with damage from different systems.

The annual incidence of RA worldwide is approximately 30 per 100,000 people and the prevalence is estimated at 1% of the general population. In Chile, a study shows a prevalence of about 0.5%. The disease can develop at any age, but has its apex between 30-55 years. Both incidence and prevalence are 3 to 4 times higher in women than in men.

The most common general laboratory abnormalities in RA are elevated erythrocyte sedimentation rate (ESR) and C-reactive protein concentration, in addition, mild to moderate anemia with characteristics of normocytic, normochromic, or sometimes iron-deprived anemia, less frequently an increase in the count can be seen platelets (thrombocytosis). All these manifestations are nothing

more than an expression of the systemic inflammatory nature of RA (Okroj *et al.*, 2007). However, in the present case, despite presenting non-confluent skin manifestations, these were not associated with joint inflammation, without the characteristic metacarpophalangeal location, and without elevation of ANA, ENA antibodies, Anti-cyclic citrullinated peptide (anti-CCP) antibody test and citrulline. The high levels of CRP and ESR, added with hypercomplementemia, to approve and compatible with the autoimmune picture of rheumatoid arthritis (Okroj *et al.*, 2007).

d) **Acronymus:** ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HIV: Human immunodeficiency virus; CMV: cytomegalovirus; EBV: Epstein Barr virus; HCV: Hepatitis C Virus; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; VDRL: Venereal Disease Research Laboratory; PPD: Purified protein derivative test; LDH: lactate dehydrogenase; CT: computed tomography; AFB: Acid-fast bacilli; AIDS: acquired immunodeficiency syndrome. Own elaboration.

3. Oncological Sphere

a) **Multiple Myeloma:** Multiple myeloma is a hematologic malignancy characterized by presence of abnormal clonal plasma cells in the bone marrow, with potential for uncontrolled growth causing destructive bone lesions, kidney injury, anemia, and hypercalcemia. No lytic bone lesions, elevation of calcemia was not taken in an evolutionary way only on admission, albumin and lactate dehydrogenase were elevated, plus gel electrophoresis showed a slight elevation of gamma proteins and hypoalbuminemia. Latest tests: Protein electrophoresis reporting hypoalbuminemia and mild hypergamma-

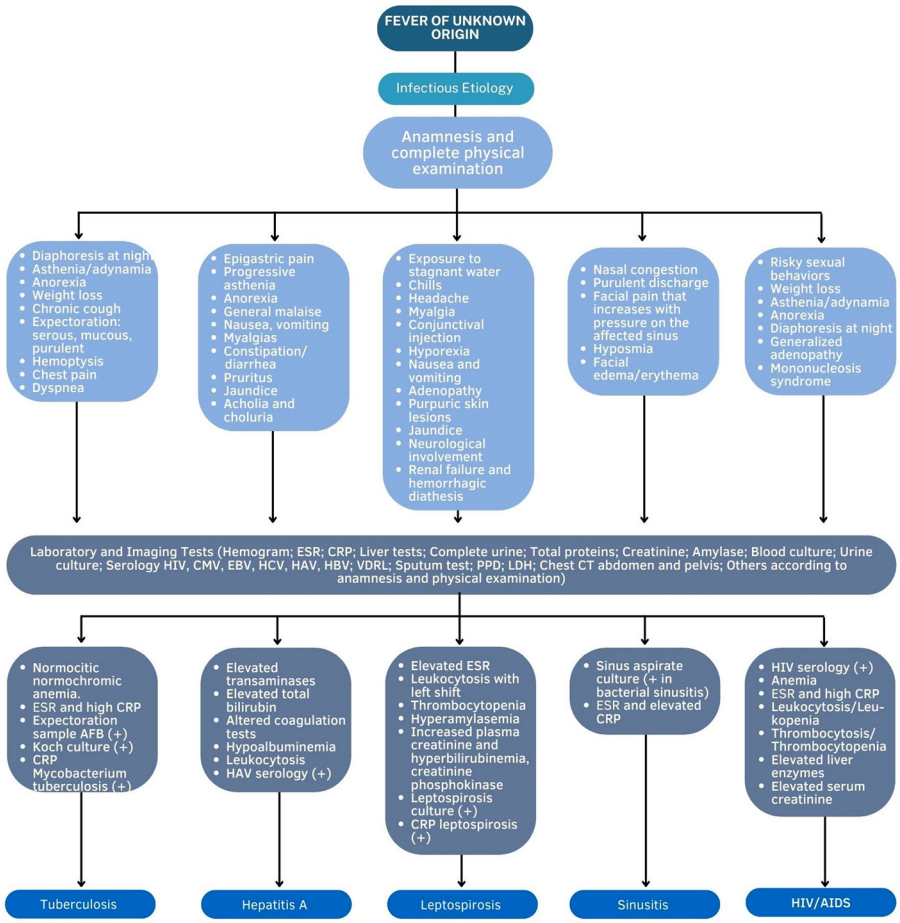

Figure 4. Outline of the management of fever of unknown origin of autoimmune etiology.

globulinemia. On 02/26/20, an endoscopy order was performed, which was performed on 03/05/20 with no pathological findings. A biopsy of the lymph nodes was also not performed to determine the degree of infiltration (Cowan *et al.*, 2022; Brigle & Rogers, 2017; Firth, 2019).

b) **Solid tumors; Testicular Cancer:** Patient manifested testicular pain and discomfort of three months of evolution due to pain and inflammation. The patient did not present loss of weight, blood in the semen, lumbar pain, or consumptive syndrome. The right testicle measures 4.2 x 2 x 2.7 cm and the left testicle 4.1 x 1.9 x 2.8 cm in its longitudinal, ap and transverse axes respectively. Epididymites of normal shape, size and echostructure. In the head of the right epididymis, 2 nodular, anechogenic, thin-walled images of 5 and 3 mm are visualized, and in the head of the left epididymis, one of similar characteristics of 2 mm. I do not see hydrocele or varicocele. When testicular cancer is in situ, it is painless, there is enlargement of the testicle, and there is an elevation of tumor markers and LDH, which can be measured with alpha-fetoprotein or Beta-Human Chorionic Gonadotropins (Beta-HCG), which was not observed in the present case (Baird *et al.*, 2018; Cheng *et al.*, 2018; Smith *et al.*, 2018).

Acronymus: ESR: erythrocyte sedimentation rate; **CRP:** C-reactive protein; **HIV:** Human immunodeficiency virus; CMV: cytomegalovirus; **EBV:** Epstein Barr virus; **HCV:** Hepatitis C Virus; **HAV:** Hepatitis A Virus; **HBV:** Hepatitis B Virus; **VDRL:** Ve-

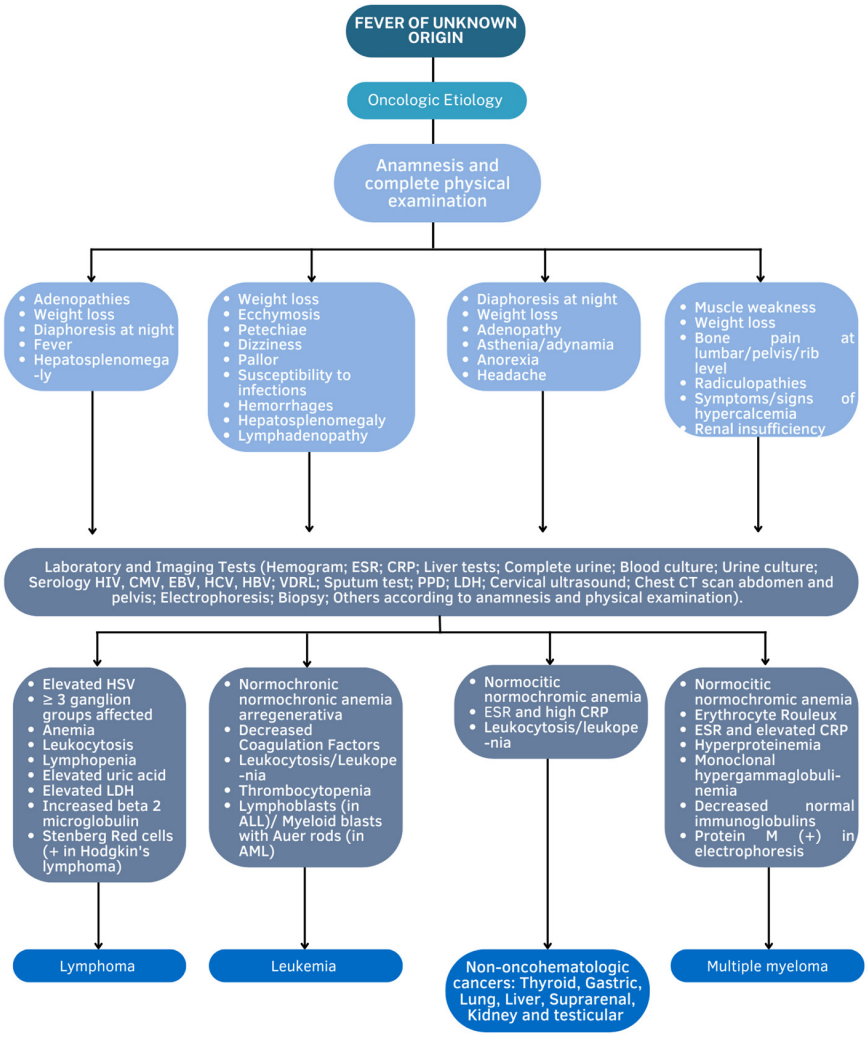

Figure 5. Outline of the management of fever of unknown origin of oncologic etiology.

nereal Disease Research Laboratory; **PPD:** Purified protein derivative test; **LDH:** lactate dehydrogenase; **CT:** computed tomography; **AFB:** Acid-fast bacilli; **AIDS:** acquired immunodeficiency syndrome; **ALL:** Acute lymphoblastic leukemia; **AML:** Acute myeloid leukemia. Own elaboration.

CONCLUSION

Case of Fever of Unknown Origin serves us as a type case to demonstrate the multiple diagnostic variables and possible etiologies that we can find, which makes it clear that we must from the beginning carry out an adequate anamnesis, an exhaustive physical examination in order to pose and thus avoid unnecessary expenses in unnecessary diagnostic tests, in order to find the most possible etiology, whether of malignant, autoimmune, miscellaneous, infectious etiology; what in our case the most possible etiology is a dermatological manifestation of the SarsCov-2 virus, which only we can hypothesize given the non-existence at the time of diagnosis of performing an antigen or CRP test, added to a possible autoimmune disease such as Wegener's syndrome, which as a result of autoimmune phenomena mediated by the cytokine storm, had not manifested presenting in this period as pustular and macular lesions that are not confluent with elevation complement , arthralgia , which at the time of diagnosis was not possible to confirm, given that specific markers such as C-ANCA antibodies can be raised not during the period of crisis but in the period of no clinical manifestation, which will require evolutivity of the picture and follow-up activity of this patient with internal medicine and a rheumatologist to achieve an adequate management of these cases.

ABSTRACT: Actually, there are more than 200 different causes of unknown fever, it is necessary for the doctor to identify the most prevalent causes of unknown fever in our environment. **Case Presentation**: A 52-year-old male patient with no history of chronic diseases, which was received in the Emergency Service of the Hospital San Pablo, Coquimbo, on 02/03/20 began a clinical picture characterized by fever up to 39 ºC associated with diaphoresis, evaluated several times in primary health care without response to symptomatic treatment. He denies dyspnea, cough, sputum production, headache, muscle weakness, myalgia, fainting, decreased visual acuity, nausea, vomiting, chest pain, abdominal pain, diarrhea, constipation, altered bowel movements, weight loss, dysuria, bladder tenesmus, pain lumbar, skin lesions. As relevant information, the patient reports having taken amoxicillin/clavulanate for 2 days on his own account. **Discussion:** Physicians should be aware of the rare extent of an unusual presentation of knowledge origin fever, probably associated with Still disease, as well as medical options for treatment. The literature does not conclude on a gold standard for the method of approach. **Conclusion:** In our case, the etiological agent that could cause Fever of unknown origin (FUO) was Sars cov-2 given the presence of elevated inflammatory factors and acute phase proteins and the presence of neutrophilic infiltration.

KEYWORDS: FUO, infection disease, autoimmune disease, sarscov-2& Still disease.

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Recibido: 24 de Julio, 2022.
Aceptado: 29 de agosto, 2022.