https://doi.org/10.15446/cr.v6n2.87649

FEVER OF UNKNOWN ORIGIN. A CHANGING CLINICAL SPECTRUM AND A DIAGNOSTIC CHALLENGE

Editorial

Moisés Casarrubias-Ramírez
Instituto Mexicano del Seguro Social
- Centro Médico Nacional La Raza -
Department of Internal Medicine
- Mexico City - Mexico.

Corresponding author
Moisés Casarrubias-Ramírez.
Department of Internal Medicine
Centro Médico Nacional La Raza.
Mexico City. México.
Email: moi.casarrubias@gmail.com

Received: 26/05/2020 **Accepted:** 02/06/2020

This issue of Case Reports presents two cases of fever of unknown origin (FUO) that illustrate the etiological diversity and diagnostic complexity of this condition. (1,2)

The world literature reports over 200 causes of FUO, including a complex mix of old and emerging diseases, as well as rare and frequent ones. In order to systematize this extensive list, the causes are usually grouped into "causal categories", which include 5 groups with some variations among the authors: infections, malignancies, inflammatory diseases, miscellaneous, and unknown causes when the etiology is not identified even after appropriate diagnostic protocols have been applied. (3) These categories, besides summarizing and systematizing the identified causes, aim to give them an etiopathogenic classification. Although this classification is useful, such a separation is artificial, and that can be seen in the articles by Prieto-Torres *et al.* (1) and González-Clavijo *et al.* (2) because the pathogenic mechanisms are similar, but the causal diseases are clearly different (a neoplasm and an inflammatory disease).

There is still no consensus on the definition of the cases. While many of the published series continue to use the criteria proposed by Petersdorf (4) in 1961, which define FUO as repeated fevers >38.3°C for a minimum of three weeks and without a clear cause after one week of studies, others accept the modifications proposed by Durack & Street in 1991 (5) about shortening the hospital stay to three days or replacing this criterion with three consecutive outpatient consultations. It should be noted that these authors (5) made a classification in which they distinguished patients with "classic" FUO from those with nosocomial fever or fever associated with human immunodeficiency virus, neutropenia, and other states of immunodeficiency. Given this scenario, in 2003, Vanderschueren *et al.* (6) raised the need to complete a protocol with a minimum number of diagnostic studies with negative results before considering a case as positive for FUO, (6) as discrepancies in the definition of the cases lead to variations and inconsistencies with respect to the distribution of causes in each of the published series.

From 1961 to date, the causes of classic FUO have gradually changed. On the one hand, there has been a relative decrease in infections and neoplasms, while a proportional increase in inflammatory diseases and cases with unknown cause has been reported. This reflects stricter patient selection and the availability of better imaging and molecular biology resources. (7-9)

Adult Still's disease, recently reclassified as an autoinflammatory disorder, accounts for a considerable proportion of the inflammatory causes reported in the most recent studies of FUO. (8,9) This is even more evident since the use of autoantibody tests (antinuclear and neutrophil antibody) has become widespread in the early stages of the study of fever, allowing earlier diagnosis of connective tissue diseases and vasculitis. The pathogenic mechanism in this condition has been associated with a cytokine storm, particularly with the production of interleukin-1, interleukin-6, and tumor necrosis factor alpha after the activation of the innate immune response. (10)

In this regard, Prieto-Torres *et al.* (1) depict the difficulty of diagnosing Adult Onset Still's Disease due to the complexity and prolonged nature of the febrile syndrome, the non-specificity of the symptoms, the lack of confirmatory laboratory tests, and the need for a diagnostic strategy by exclusion. Similarly, the article addresses another dilemma related to FUO: at some point, despite having a margin of uncertainty in the diagnosis, there will be sufficient evidence to try a therapeutic approach (in this case with steroids) that reverses the fever and confirms the diagnosis.

In contrast, as evidenced by González-Clavijo *et al.*, (2) the patient with FUO secondary to a pheochromocytoma represents other aspects of interest, since it highlights the usefulness of early imaging studies (abdominal ultrasound) in the approach to fever and anatomo-functional localizers (fluorodeoxyglucose positron emission tomography + computerized axial tomography) to study suspicious anatomical lesions and plan confirmatory studies, either directed or excisional biopsies. (11) Likewise, the study of this type of patient allows for a better analysis of the crossroads of the causal mechanisms of fever, since pheochromocytoma can be an endocrine, neoplastic, and inflammatory cause at the same time.

Pheochromocytomas have been related to several mechanisms of hyperthermia that go from the hyperadrenergic state, caused by catecholamine-producing variants, to the proinflammatory state of interleukin-6-producing variants, as occurred in the case presented by González-Clavijo *et al.* (2)

In conclusion, FUO continues to be a diagnostic challenge that requires an individualized approach based on data obtained from clinical records and basic laboratory and specialized studies. In addition, such data must be supplemented by clinical judgement that, in a balanced way, is based on evidence and experience.

REFERENCES

1. **Prieto-Torres AE, Suárez-Molina W, Pantoja-Agreda JI.** Adult Onset Still's Disease (AOSD): A rare condition with a classic clinical presentation. Case Report. *Case Reports*. 2020;6(2).
2. **González-Clavijo AM, Fierro-Maya LF, Muñoz-Loaiza JD, Guzmán-Rojas JD, Vanegas-Antolinez JJ, Bermúdez-Silva LN.** Pheochromocytoma presenting as fever of unknown origin, a case report. *Case Reports*. 2020;6(2).
3. **Wright WF, Auwaerter PG.** Fever and fever of unknown origin: review, recent advances, and lingering dogma. *Open Forum Infect Dis.* 2020;7(5):ofaa132. http://doi.org/d2jf.
4. **Petersdorf RG, Beeson PB.** Fever of unexplaines origin: report on 100 cases. *Medicine (Baltimore).* 1961;40:1-30. http://doi.org/ccwft6.
5. **Durack DT, Street AC.** Fever of unknown origin, reexamined and redefined. *Curr Clin Top Infect Dis.* 1991;11:35-51.
6. **Vanderschueren S, Knockaert D, Adrianssen T, Demey W, Durnez A, Blockmans D, *et al.*** Frome prolonged febrile illness to fever of unknown origin: The challenge continues. *Arch Intern Med.* 2003;163(9):1033-41. http://doi.org/fqk44d.
7. **Bleeker-Rovers C, Vos FJ, De Kleijn EMHA, Mudde AH, Dofferhoff TSM, Richter C, *et al.*** A prospective multicenter study of fever of unknown origin. *Medicine (Baltimore).* 2007;80(1):26-38. http://doi.org/d2jf.
8. **Shang J, Yan L, Du L, Liang L, Zhou Q, Liang T, *et al.*** Recent trends in the distribution of causative diseases of fever of unknown origin. *Wien Klin Wochenschr.* 2017;129(5-6):201-7. http://doi.org/f9zxq4.
9. **Casarrubias-Ramírez M, Alfaro-Mefía JA, De Santiago Leaños J, Mendoza-Álvarez SA, Pineda-Galindo LF, Vera-Lastra OL.** Fiebre de origen oscuro, comparación de dos series con 26 años de diferencia. *Rev Med Ins Mex Seguro Soc.* 2015;53(Suppl 1):6-17.
10. **Ludwig DR, Amin TN, Manson JJ.** Suspected systemic rheumatic diseases in adults presenting with fever. *Best Practice & Research Clinical Rheumatol.* http://doi.org/d2qs.
11. **Cheng X, Zhang M, Xiao V, Li H, Zhang Y, Ji Z.** Interleukin-6 producing pheochromocytoma as a new reason for fever of unknown origin. *A retrospective study. Endocr Pract.* 2018;24(6):507-11. http://doi.org/d2f6.