Comments on: Neoplastic Fever- All who Shivers are not Infected

Ankur Dalal
Assistant Professor in Medicine, The Sarvajanik Medical Trust Hospital, Surat, Gujarat

Sir,

I have read the case report titled, "Neoplastic Fever - All who shivers are not infected" written by Sharma YB et al.[1] with great interest. The authors suggest that any case presenting with acute fever not responding to standard line of treatment and having all primary routine investigations normal, work up for neoplasm as a cause of fever should be kept in mind.[1] However, there are few clarifications needed for the common readers, which I would like to highlight.

First of all, clinician commonly refers to any febrile illness without an initially obvious aetiology as fever of unknown origin (FUO).[2] Now a day as better diagnostic techniques; including CT and MRI are widely available, only the cases that are more difficult to diagnose continue to meet criteria for classical FUO. The authors had mentioned in their conclusion about 'acute fever not responding to standard line of treatment'. I would like to emphasise here that there is nothing like standard line of treatment for FUO, instead the treatment should be individualised. Now looking in to this particular case antibiotic (ceftriaxone) and antimalarial (artesunate), both treatments were started as empirical on presentation. Then after two days just because fever was not subsided even in absence of vital-sign instability change of antibiotic (ceftazidime) and antimalarial (quinine) were done. This approach was not explainable. As we know that both antibiotics are third generation cephalosporins and the major difference is useful activity against pseudomonas aeruginosa for ceftazidime. So, whether authors suspected this particular organism clinically, which led them to switch over to this molecule was not specified (as per authors they considered higher antibiotic but actually one of parameter to select antibiotics is suspected organism/spectrum of organisms). Similarly in this particular case patient's peripheral smear for malaria parasite was already negative, total count was raised (which is unusual for malaria) and there was no reason to suspect artemisinin resistance malaria; but still antimalarial was changed, which is also not convincing.

The emphasis in patients with FUO is on continued observation and examination, with the avoidance of "shotgun" empirical therapy. The antibiotic therapy, (even for tuberculosis) may irrevocably alter the ability to culture fastidious bacteria or mycobacterium and delineate ultimate cause. However, vital-sign instability or neutropenia is an indication for empirical therapy.[2] Similarly as per WHO guideline artimisinin should not be used as monotherapy, as this will promote resistance to this critically important class of antimalarials. It is also recommended that if malaria is suspected clinically and decision to treat is made, then a full effective treatment which has been started should be completed even the diagnosis is not confirmed by test.[3]

Second, the authors discussed that in appropriate clinical settings, therapeutic trials of antitubercular drugs may be accepted. It is particularly helpful in cases where there is a history of prolonged low-grade fever with evening rise along with raised ESR, a positive tuberculin test.[1] However, they themselves started empirical antitubercular drugs in this particular patient with a very short duration of high-grade fever with negative tuberculin test just considering high ESR, which was also not convincing. If the tuberculin test is positive or if granulomatous hepatitis or other granulomatous disease is present with anergy (and sarcoid seems unlikely), then only a therapeutic trial for tuberculosis should be undertaken for classical FUO, with treatment usually continued for up to 6 weeks. A failure of the fever to respond over this period suggests an alternative diagnosis.[2]

Third, authors discussed about "naproxen challenge", which may be useful in evaluating prolonged fever suspected to be of neoplastic origin. However, author did not provide any references in support, which can be useful in clinical practice. Vanderschueren S et al.[4] concluded that naproxen test is not specific for tumor-related fever and has no differential diagnostic role in the work-up of a patient with prolonged unexplained fever from their study. Ampel NM et al.[5] also commented after reviewing Vanderschueren S et al.[4] at NEJM journal watch that although the study was retrospective and few subjects had a malignancy, the results indicate that the naproxen test is neither sensitive nor specific for distinguishing cancer from other etiologies of occult fever. This makes sense, since the antipyretic mechanism of NSAIDs is independent of the etiology of the fever.

On concluding my comments; in my opinion the conclusion of standard line of treatment for acute unexplained fever; which was shown in this case, cannot be recommended as a general approach in routine practice as discussed above. I also opine that instead of in its presentation, uniqueness of the case is actually lies in its disease entity as anaplastic large cell lymphoma (ALCL) is a rare type of non-hodgkin's lymphoma and primary involvement in the central nervous system of ALK positive ALCL, however, is even rarer or exceptional.[6]

References

1. Sharma YB, More AV. Neoplastic Fever- All who shivers are not infected. *Journal of The Association of Physicians of India* 2017; 65: 94-95.
2. Bleeker-Rovers CP, Van der meer Jos WM. Fever of Unknown Origin. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, editors. In: Harrison's Principles of Internal Medicine. 19th ed. United States of America: The McGraw-Hill Companies Inc.; 2015. p.135-42.
3. WHO. Guidelines for the treatment of malaria. Second edition. World Health Organization, Geneva; 2010.
4. Vanderschueren S, Knockaert DC, Peetermans WE, Bobbaers HJ. Lack of value of the naproxen test in the differential diagnosis of prolonged febrile illnesses. *Am J Med* 2003; 115:572-5.
5. Ampel NM. Don't Judge a Fever by its Response to Naproxen. NEJM Journal watch November 24, 2003.
6. Park JS, Park H, Park S, Kim SJ, Seol HJ, Ko YH. Primary Central Nervous System ALK Positive Anaplastic Large Cell Lymphoma with Predominantly Leptomeningeal Involvement in an Adult. *Yonsei Medical Journal* 2013; 54:791-796.