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Hematological "red flags" for disseminated tuberculosis: A diagnostic opportunity for the emergency physician?

In the modern era, the following are the most useful strategies available to emergency physicians to expedite timely validation of a provisional diagnosis of disseminated tuberculosis(TB) in a febrile patient with a normal chest X-ray:-

Computed tomography of the thorax to document miliary tuberculosis [1], mycobacterial blood culture and polymerase chain reaction (PCR) of a peripheral blood sample for *M tuberculosis* DNA [2], urinary diagnostics using PCR of the urine for *M tuberculosis* DNA and evaluation of urinary lipoarabinomannan(LAM) [3].

This diagnostic pathway is typically activated when there is a high index of suspicion for disseminated TB. The index of suspicion can be raised by certain hematological stigmata identifiable in a peripheral blood sample, including hemophagocytosis(so-called hemophagocytic syndrome(HS)), and disseminated intravascular coagulation(DIC), both of which confer an adverse prognosis.

In a world literature review of 37 cases of tuberculosis-associated-HS, there were 29 cases that received some form of antituberculous therapy. Only 19 survived. In most cases treatment failure was attributed to treatment delay [4]. In another series, comprising 8 cases of TB-associated HS, six of whom died, the use of mycobacterial blood culture was documented in only 2 cases, and no mention was made of PCR evaluation of a peripheral blood sample or urinary diagnostics [5]. However, in one reported instance, a timely response to the recognition of the association between HS and disseminated TB may have been life-saving:-

This was a 36 year old woman who presented with fever, lymphadenopathy, and pancytopenia. The presence of haemophagocytosis in the peripheral blood sample prompted evaluation of a peripheral blood sample by mycobacterial culture and by PCR for *M tuberculosis* DNA. Both tested positive for *M tuberculosis* [6].

Stigmata of tuberculosis-associated DIC are also identifiable in a peripheral blood sample. The coexistence of DIC and miliary TB is reportedly associated with a mortality of 70.6%, typically attributable to acute respiratory failure [7]. The association of miliary TB and DIC also confers a risk of peripheral symmetrical gangrene [8]. Testifying to the benefit of prompt recognition of the significance of DIC for timely diagnosis of disseminated TB is the following report of tuberculosis–associated DIC:-

A 21 year old woman presented with fever and weight loss. Her chest X-ray was normal. The subsequent development of florid stigmata of DIC, and derangement of liver function tests raised the index of suspicion for disseminated TB. The latter diagnosis was supported by a subsequent CT of the thorax which showed evidence of miliary TB. CT of the cervical region showed lymphadenopathy, prompting needle biopsy under ultrasound guidance. The latter yielded acid fast bacilli consistent with *M tuberculosis*. The patient responded well to antituberculous chemotherapy [9].

Disseminated tuberculosis can also present with pancytopenia [10,11],which, in some cases may be associated with HS, the latter evident only in the bone marrow aspirate [12-14]. One of those examples was a 9 year old girl who presented with fever and weight loss. In spite of an initially normal chest X-ray and a peripheral blood hemogram which showed pancytopenia in the absence of HS, bone marrow examination showed stigmata of HS. A repeat chest X-ray showed miliary shadowing, and *M tuberculosis* was cultured from early morning gastric aspirate [12]. The coexistence of stigmata of HS in the bone marrow, in the absence of HS in the peripheral blood film, was also a feature in an 18 year old woman who had pancytopenia and coexisting DIC. Thoracic CT showed bilateral lung infiltrate with superimposed miliary shadowing most consistent with miliary TB. Although her extensive work-up did not include mycobacterial blood culture or PCR of the peripheral blood for *M tuberculosis* she did receive the benefit of a diagnostic trial of antituberculous chemotherapy to which she responded remarkably well [13]. The fatal consequences of diagnostic delay were exemplified by a 75 year old hemodialysis patient who presented with fever and a chest X-ray which showed fibronodular shadowing in the left upper lobe. Two weeks after admission he developed pancytopenia(without concurrent HS in the peripheral blood sample), but it was only three weeks later that he had a bone marrow examination. The bone marrow aspirate showed stigmata of HS. Bone marrow biopsy revealed many epitheloid granulomas some of which contained acid fast bacilli. PCR of the bone marrow also tested positive for *M tuberculosis* DNA. Antituberculous chemotherapy was then initiated but he died 3 days after he commenced treatment [14].

Comment

Hematological red flags for potentially lethal complications of disseminated tuberculosis include HS, DIC, and pancytopenia. In a limited resource setting even limited activation of the diagnostic pathway for disseminated TB can expedite empiric treatment of disseminated TB [13], thereby saving lives. Conversely, a delay in identifying HS as the underlying cause of either disseminated TB or tuberculosis-related pancytopenia might prove fatal [14].

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Oscar M.P. Jolobe, MRCP
Manchester Medical Society, Simon Building, Brunswick Street, Manchester M13 9PL, United Kingdom of Great Britain and Northern Ireland
E-mail address: oscarjolobe@yahoo.co.uk.

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Chlamydia and gonorrhea screening in the ED setting: increasing evidence of utility and need for further research

I applaud the work of Garlock et al. in investigating the utility of chlamydia (CT) and gonorrhea (GC) screening in emergency departments (ED). In the time of record levels of these infections and the specter of antimicrobial resistant gonorrhea (AMR GC) on the horizon, new means to identify and treat those at risk are sorely needed [1-3].

I would like to point out that somewhat similar work has been done before, and complements to a large extent the findings presented by this study. Two of our previous studies of prospective screening of emergency department patients found both relatively high rates of infection and individual-level factors suitable to refine screening criteria. The first study of universal urine-based screening of females aged 15–35 years for CT/GC found a disease prevalence of 9.1% (CT only 5.7%; GC only 2.5%; CT and GC 0.9%) [4]. Further, restricting screening to only those "…reporting *2+ male partners in the past year* or those *who thought their sex partner had other partners* resulted in a 52% decrease in the number of tests administered and a 73% increase in screened patient prevalence." Our second universal screening study, including males and oropharyngeal swabs in additional to urine specimens, found an overall prevalence of 7.7% with similar risk between males and females [5]. Further, 26.3% of infected individuals had an oral infection, and the majority of oral GC infections would not be identified with urine-based screening. Both of these studies were pilots at a single hospital site and require further exploration.

The clinical setting (primary and emergency) has been and will likely continue to be a critical aspect of addressing sexually transmitted disease screening and treatment [6,7]. Still, universal screening in relatively low prevalence settings is not generally considered cost-effective [8].

As Hull et al. describe in their review, there are multiple factors impacting both cost-effectiveness and even full implementation of current guidelines [8]. Of particular concern for emergency department-based screenings is the potential loss to follow up, leading to presumptive treatment as a frequently-preferred paradigm. While efficient from an operations perspective, it is unattractive in terms of waste, potential for inadequate treatment (for those truly infected), and adverse personal and social outcomes (for those not infected). Whereas the primary care setting has an established framework for long-term patient engagement and follow up, none such exists in the emergency setting. Models of linkages between ED-based screening and other agency follow up and treatment have been explored, and I would suggest that further study in this regard is warranted [9,10]. While truly new strategies for addressing increasing rates of STDs and AMR GC are needed, expanding and refining evidence-based practices in existing clinical sites may be comparably low cost and easily generalized.

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Wiley D. Jenkins, PhD, MPH, FACE[1,2]
Southern Illinois University, School of Medicine, 201 E. Madison Street, Springfield, IL 62794-9664, United States of America
E-mail address: wjenkins@siumed.edu.

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Red cell distribution width and mean platelet volume in carbon monoxide poisoning

Dear Editor,

We read the article "Predicting of neuropsychosis in carbon monoxide poisoning according to the plasma troponin, carboxyhemoglobin (COHb), red cell distribution width (RDW) and mean platelet volume (MPV) levels" by Coskun et al. [1] They aimed to determine the predictivity of neuro psychosis in carbon monoxide poisoning by the admission levels of RDW, MPV and troponin I levels which can be measured quickly and easily in the emergency department (ED). They

[1] Chief, Epidemiology and Biostatistics, Department of Population Science and Policy.
[2] Associate Professor, Family and Community Medicine.