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CASE REPORT

Think global, act local: chronic dysuria and sterile pyuria in an Eritrean-American woman

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SUMMARY

A 70-year-old female Eritrean immigrant living in the USA presented with classic findings of genitourinary (GU) tuberculosis (TB), including risk of tuberculosis exposure based on country of origin, chronic urinary tract symptoms and persistent sterile pyuria despite antibacterial therapy. Furthermore, this patient had the hallmark radiographical findings of ureteral stricture, a dilated pelvic calyceal system, hydroureteronephrosis and bladder wall thickening, as well as a bladder wall biopsy that revealed granulomatous disease. The patient was evaluated multiple times over the course of 3 years in outpatient and inpatient medical settings before a diagnosis was made and appropriate treatment initiated. As with many cases of GU TB, a protracted diagnosis allowed for advanced disease progression and significant morbidity from obstructive uropathy and chronic kidney disease.

BACKGROUND

Because of its protean presentation and frequent mimicry of other common genitourinary (GU) pathologies, GU tuberculosis (TB) is often an under-recognised diagnosis. This is perhaps most significant in developed countries where active pulmonary TB prevalence has declined markedly and new medical trainees may not have the experience to recognise diagnostic features of extrapulmonary disease. Underdiagnosis may be further compounded by the fact that the populations at highest risk for TB within these countries, including immigrants, the marginally housed, immunocompromised patients and prison inmates, are often medically underserved. Furthermore, clinicians may not realise that worldwide the GU tract is the second most common organ system impacted by disseminated TB. Thus, in order to limit potentially severe morbidity, it is important for medical providers to recognise the classic characteristics of GU TB.

CASE PRESENTATION

A 70-year-old Eritrean woman initially presented to an outpatient clinic with dysuria, haematuria and chills. The patient immigrated to the USA in 2001 and returns to Eritrea regularly to visit family. She never smoked tobacco, drank alcohol or used any illicit substances. She lives with her daughter and grandchild. No other family members have acute or chronic medical illness and there are no animals in their home. Urinalysis obtained at her initial visit demonstrated more than 50 red blood cells per high power field (HPF), more than 50 white cell count/HPF and a positive leucocyte esterase. The general practitioner made a presumptive diagnosis of uncomplicated cystitis and started the patient on empiric antibiotic treatment with oral cephalexin. Her urine culture ultimately returned negative.

The patient's symptoms persisted and she received multiple courses of oral and intravenous antimicrobials for presumed recurrent bacterial urinary tract infections. Notably, urinalyses obtained at each visit demonstrated haematuria, pyuria and proteinuria but urine cultures continually returned negative. Over the course of 3 years, the patient had a total of 17 negative urine cultures documented in her medical record. Cytological examination of specimens from voided urine and bladder irrigation demonstrated atypical cells with mixed inflammation but no malignancy. After a thoughtful review of her disease course and social history, it became evident that the combination of an appropriate exposure (East African origin), chronic progressive lower urinary tract symptoms and persistent sterile pyuria despite antimicrobial therapy constituted features concerning GU TB. Acid-fast bacilli (AFB) culture of her urine was performed, and ultimately all four samples returned positive for *Mycobacterium tuberculosis*.

INVESTIGATIONS

In the three years prior to her diagnosis, our patient underwent several radiographical and urological studies. Abdominal ultrasound was performed first and showed bilateral left greater than right hydronephrosis, left caliectasis and bladder wall thickening. CT of the abdomen and pelvis subsequently confirmed bladder wall thickening, moderate left hydroureteronephrosis and diffuse ureteral enhancement with an enlarged left retroperitoneal lymph node (figure 1A,B). This was followed by a left retrograde pyelogram that demonstrated a moderately dilated left pelvic calyceal system with a long segment stricture of the distal left ureter (figure 1C). Cystoscopy and ureteroscopy revealed an abnormal non-papillary urothelium and friable bladder epithelium. Biopsy of the bladder wall showed mixed acute and chronic inflammation with non-necrotising granulomas (figure 2) that stained negative for AFB. Notably, the patient's chest X-ray demonstrated clear lungs with no nodules or cavitary lesions.

The radiographical findings in GU TB directly reflect the underlying infectious pathophysiology (figure 3). Because of the intrinsically slow disease

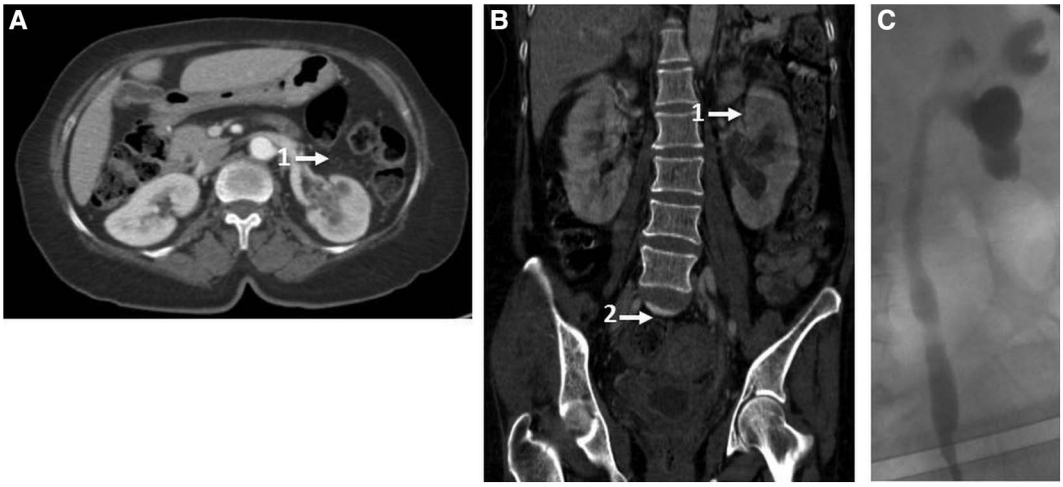

Figure 1 CT of the abdomen and pelvis (A and B) demonstrating moderate left hydroureteronephrosis (arrow 1) and a thickened bladder wall (arrow 2). Left retrograde pyelogram (C) demonstrating a moderately dilated left pelvic calyceal system with a long stricture of the distal left ureter.

progression and delays in diagnosis, the radiographical findings are variable and highly dependent on the extent of organ involvement. Intravenous urography and abdominal and pelvic CT scanning are the most frequently employed imaging techniques, although ultrasound findings characteristic of GU TB in the correct setting have also been described.[1]

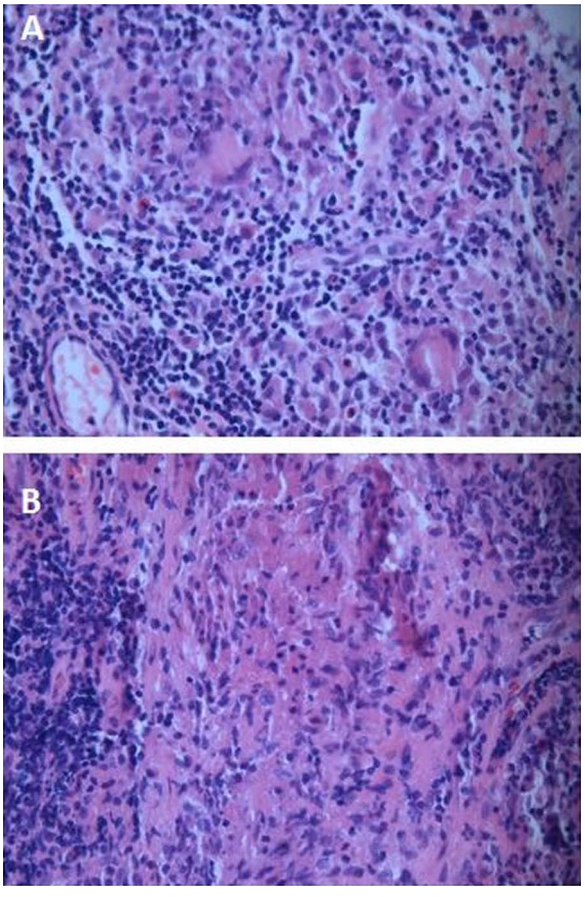

Figure 2 H&E stains at ×40 magnification depicting caseating (A) and non-caseating (B) granulomas identified in tissue from bladder wall biopsy. GMS stain revealed no acid-fast bacilli.

CT and intravenous urography findings typically seen in GU TB include: irregularity of the caliceal outline due to necrotising papillitis (described as 'moth-eaten', often an early finding), thickening of the collecting system, calcification of the urinary tract, stenosis-related dilation of the collecting system with hydrocalycosis/nephrosis and/or hydroureter, renal masses, parenchymal atrophy and bladder contraction.[1–5] In particular, the presence of multiple ureteral strictures is a pathognomonic finding in GU TB, and a single stricture with at least one of the findings listed above (as seen in the patient described here) or evidence of autonephrectomy plus one other imaging finding except stricture can be seen in more than 94% of intravenous urography and CT studies.[6] Ultrasound can also be utilised for GU TB evaluation; however, this method is less sensitive and specific and typically not recommended.

Microbiological evaluation of GU TB is usually initiated (as in the case of this patient) because of a patient's epidemiological risk factors combined with multiple, non-specific urinary symptoms and otherwise unexplained findings (including sterile pyuria). AFB stains are commonly utilised as an initial diagnostic modality. Modified Ziehl-Nielsen or auramine-rhodamine staining for AFB on centrifuged urine cells can be performed in less than 1 h; however, this method lacks sufficient sensitivity and requires 10^4–10^6 bacilli/mL of urine for a positive test. AFB culture of at least three early morning (complete first void) urine samples is the diagnostic modality of choice, requires 10^3 fewer bacilli/mL compared with staining and has a specificity of 100%. Unfortunately, sensitivity is variable, ranging between 10% and 80%, and is highly dependent on disease severity and sample preparation technique.[7–12] Furthermore, AFB cultures may take up to 8 weeks to become positive. If the patient has taken fluoroquinolones for treatment of presumed bacterial urinary tract infections (UTIs), this may also delay GU TB diagnosis given the antituberculous activity of fluoroquinolone antibiotics. In the case presented here, the patient's diagnosis was initially confirmed after four out of four first void urine AFB cultures returned positive, the first after just 15 days of culture.

Nucleic acid amplification tests (NAATs) are becoming more frequently available and offer a rapid molecular method to complement culture and stain-based diagnostic techniques.[9] NAATs can be performed on any sample substrate and target several sequences unique to *M tuberculosis*. Sensitivities for NAATs in urine range from 87% to 100%, with specificities of 92–99.8%.

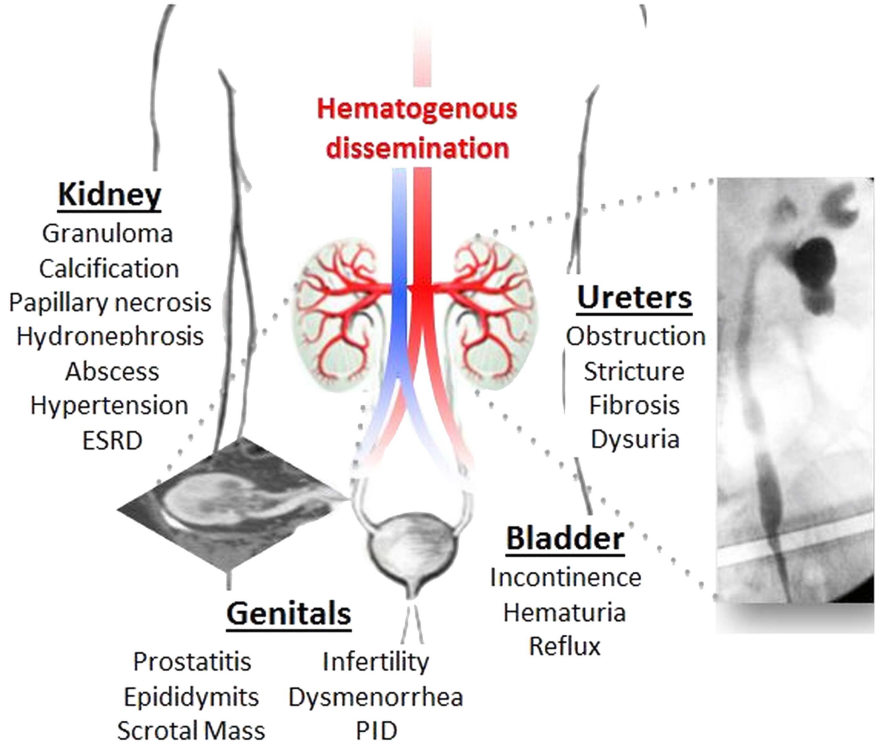

Figure 3 Symptoms and pathological findings of the genitourinary organs affected by *Mycobacterium tuberculosis*.

Importantly, this methodology allows one to detect genes or specific mutations conferring drug resistance to common first-line anti-TB chemotherapies.[7 13 14] Limiting factors for NAATs include false negatives due to amplification inhibition by urinary enzymes and false positives in patients undergoing active therapy despite effective treatment response.[1 9 15]

Microbiological diagnosis can also be obtained by renal biopsy of granulomatous lesions. Histiocytes and granulomas are commonly observed on pathological examination of fine-needle aspirate preparations. While stain and culture of tissue biopsy is highly specific, it is compromised by poor sensitivity, estimated at only 18% to 45% (as demonstrated by the fact that this patient had negative AFB staining of her bladder biopsy samples). Moreover, the culture of biopsied material offers no time advantage over urine AFB culture and may confer significantly greater morbidity from the sample collection. The majority of the value of biopsy is related to the exclusion of malignancy.[1 16]

Despite an encouraging, albeit modest, decline in the global prevalence of TB over the past century, the emergence of multi-drug-resistant-TB has become a major public health concern, with the rate of resistant cases doubling in the past two years in countries with the highest TB burdens.[17] Because of this, obtaining drug susceptibilities prior to initiation of treatment is highly beneficial in endemic areas with known resistance.[7]

DIFFERENTIAL DIAGNOSIS

This patient presented with chronic sterile pyuria despite repeat treatment with broad spectrum antibiotics. In many cases, partially treated bacterial UTIs can result in sterile pyuria as can improper clean-catch sampling of midstream micturition. Other non-infectious intrinsic renal causes of sterile pyuria include papillary necrosis (eg, obstructive uropathy, diabetic nephropathy) and tubulointerstitial diseases (eg, interstitial nephritis, lupus nephritis). GU structural abnormalities causing sterile pyuria include polycystic kidney disease, vesicourethral reflux, nephro/urolithiasis, hydronephrosis and urinary catheters. Nephrotoxic medications are a notable cause of sterile pyuria, and common inciting agents include non-steroidal anti-inflammatory drugs (NSAIDs), cyclophosphamide, steroids and indinavir. Notable systemic conditions that may lead to sterile pyuria include severe hypertension, sarcoidosis, systemic lupus erythematosus, pregnancy and malignancies including renal and bladder carcinomas. Infectious causes of sterile pyuria include fastidious organisms such as *Ureaplasma urealyticum*, sexually transmitted infections (*Chlamydia trachomitis*, *Neisseria gonorrhea*, *Trichomonas vaginalis*, herpes simplex virus), parasitic infections (*Schistosoma haematobium*), and in men, prostatitis and balanitis. Finally, uncommon bacterial infections, in particular those due to *M. tuberculosis*, are an important cause of persistent sterile pyuria and require a fair amount of clinical suspicion to make the diagnosis.[18]

To help differentiate the potential aetiologies of sterile pyuria in this patient, the following studies had previously been sent and returned negative: urine cytology, bladder epithelial biopsy (negative for malignancy) and anti-Schistosoma antibodies. After reviewing the results of our patient's prior testing and imaging, and considering her risk factors for TB exposure, sending urinary AFB cultures to evaluate for GU TB was the most reasonable step.

TREATMENT

Pathogen eradication in GU TB lacking drug-resistance mutations is based on the standard first-line treatment regimen utilised for active pulmonary disease and recommended by the WHO.[19] This regimen incorporates an initiation phase with 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol, dose-adjusted for renal function and body mass, followed by a 4-month maintenance phase of rifampicin and isoniazid.[20 21] Different agents and potentially longer treatment are required if MDR TB or extensively drug resistant (XDR) TB is present or if intolerance due to side effects occurs. Isoniazid resistance is estimated to occur in 10% of all TB cases worldwide. Resistance to more than one agent is also increasing at an alarming rate, and

accounts for 3.7% of infections worldwide.[17] More than 60% of these cases occur in just three countries: China, Russia and India. PCR-based testing is being increasingly utilised to allow for early detection of MDR strains by rapidly identifying genes and discrete point mutations that confer drug resistance.[7]

Treatment of TB in HIV-positive individuals also requires careful consideration. Co-infection of TB with other pathogens combined with impaired cellular immunity may result in protracted disease recovery. Furthermore, the clinician should be aware of paradoxical symptom exacerbation resulting from immune reconstitution inflammatory syndrome in patients with AIDS undergoing simultaneous antiretroviral and antitubercular therapy.[7 22 23] The treatment course of GU TB may also be complicated by medication-induced nephrotoxicity. In addition to the well-known hepatotoxicity of antitubercular therapy, rifampicin alone can induce tubular and interstitial injury resulting in acute renal failure, glucosuria and nephrogenic diabetes insipidus.[7]

In patients with extensive renal complications, surgical procedures can augment medical therapies and also allow for functional restoration of damaged organs.[7 24 25] Abscesses that fail to resolve with pharmacological intervention alone can be drained surgically. In patients with problematic hydronephrosis, percutaneous nephrostomy, stenting, endoscopy or balloon dilation may be utilised to relieve obstruction. Nephrectomy is indicated when the disease course has resulted in severe hypertension, is accompanied by malignancy or chronic pain, or in the event of site-specific disease recurrence.[7 22] In severe cases, anastomotic procedures or reconstructions of the ureters, bladder and genitals may be performed.[23 26–28] With improvements in anti-tubercular chemotherapeutics and mycobacterial diagnostics, surgical interventions are less common now compared with prior decades.

OUTCOME AND FOLLOW-UP

By the time of treatment initiation, the patient's previously mild lower urinary symptoms progressively worsened and became complicated by gross haematuria, urge incontinence and polyuria. Fortunately, resistance testing confirmed a pan-susceptible organism. The patient's treatment was intermittently interrupted and consequently protracted due to medication-related nausea and emesis requiring multiple adjustments of her pharmacological regimen. Her ureteral strictures worsened, leading to severe hydronephrosis, acute kidney injury and ultimately stage three chronic kidney disease (CKD). She was subsequently admitted to the hospital for hyperkalemia associated with electrocardiogram (ECG) abnormalities, as well as haematuria. She received bilateral J stent placement to compensate for her ureteral strictures and is currently undergoing outpatient management by a nephrologist and a urologist. Presently, her most notable residual symptom is urinary frequency and incontinence secondary to a contracted bladder (estimated capacity of 50 milliliters). Fortunately, a tolerable treatment regimen was eventually identified and follow-up AFB urine cultures after four months of therapy returned negative, confirming successful microbiological control of her infection.

DISCUSSION

Epidemiology of GU TB

TB is a major cause of morbidity and mortality worldwide, with more than eight million new infections each year and over one-third of the world population being currently infected with the disease. This results in two million annual deaths from severe infections, a number second only to HIV/AIDS in terms of global infection-related mortality.[19] The highest prevalence of TB exists in developing countries, including India, China, Russia, eastern Europe, southeast Asia and much of Africa.[25 29 30] In the USA in 2011, a total of 10 528 cases of newly diagnosed TB were reported (rate of 3.4 cases/100 000 persons).[31] The prevalence among foreign-born persons is approximately 11.5 times higher when compared with US-born persons (17.2 vs 1.5 cases/100 000).[32]

Worldwide, extrapulmonary disease is seen in 4.5–47.9% of primary TB cases, and of these GU involvement is found in 40% of instances.[7 33–35] An evaluation of extrapulmonary TB cases in the USA between 1993 and 2006 found that GU TB cases constituted only 6.5% of the reported extrapulmonary cases, with similar findings in surveillance reports from EU countries.[34 36] Given the fact that making a diagnosis of GU TB is challenging, these numbers most likely vastly underestimate the true number of such cases. In general, the prevalence of extrapulmonary disease is higher in populations with compromised immune function and may be found in up to 50% of HIV-positive patients with pulmonary TB.[7 37 38] Extrapulmonary TB is also more prevalent in other patient groups with impaired cellular immunity, including solid organ transplant recipients, patients receiving immune-modulating agents and those with end-stage renal disease (ESRD) on haemodialysis.[25 39]

Pathophysiology and clinical presentation of GU TB

GU TB is characterised by non-specific symptoms and clinical findings that can mimic other GU pathologies (figure 3). Lower abdominal pain, urinary frequency, haematuria and/or pyuria may be mistaken for common cystitis, and patients rarely demonstrate the fevers or systemic symptoms classically seen in pulmonary TB.[40] Because of this, patient symptoms are frequently attributed to other disease processes resulting in a delayed GU TB diagnosis and unnecessary morbidity including irreversible kidney damage.[41]

In two-thirds of cases, GU TB is a result of reactivation after resolution of primary pulmonary mycobacterial infection; however, it can also present as a feature of primary disseminated TB.[40 42] In both instances, organisms spread from the lungs to the kidneys via haematogenous dissemination, with subsequent involvement of the ureters and bladder through descending infection of the collecting system and genital organs.[43 44] As in this patient, reactivation of latent TB may occur many years after primary infection and most patients have no pulmonary symptoms. Furthermore, at the time of diagnosis of GU TB, only one in three patients have abnormal chest X-ray findings.[40 42 45–47]

CKD and ESRD can progress insidiously and complicate an estimated 20–50% and 5–20% of GU TB cases, respectively.[35 38 48–50] In many instances, inflammatory damage and granuloma formation lead to papillary necrosis, ulceration of the calyces, calcification and eventual destruction of the renal parenchyma. An obstructive uropathy can also occur due to ureteral localisation of infection and associated inflammation, fibrosis, stricture formation and hydronephrosis.[7 51] Inflammation-induced ischaemia results in activation of the renin-angiotensin cascade, which can induce refractory hypertension that in severe cases may require nephrectomy for treatment.[7] Inflammatory changes may also affect the bladder, eroding the urothelium and inducing fibrosis, decreased bladder capacity, and incontinence.[7]

GU TB can also impact the reproductive organs and cause irreversible damage leading to infertility in men and women. In men, GU TB can result in infertility, urethritis, prostatitis and epididymitis. Almost 50% of men present with clinical abnormalities in the scrotum such as a palpable mass, beading of the

spermatic cord, scrotal wall thickening or a moderate hydrocele.[35] Severe reproductive organ disease is most common in female patients and may present with fulminant symptoms resembling pelvic inflammatory disease or manifest with more generic findings including chronic pelvic pain and dysmenorrhoea long after infection clearance. In some countries, GU TB may account for 1% of postmenopausal uterine bleeding and 60–94% of infertility, making this disease a leading consideration during evaluation for reproductive difficulty in certain regions.[7 52–56] Even after treatment, less than 10% of births in patients with diagnosed GU TB are successful.[7 57] Timely diagnosis and appropriate consideration of this underappreciated and often insidious TB manifestation will prevent significant unnecessary morbidity worldwide.

Learning points

- There are more than eight million new tuberculosis (TB) infections each year and over two million annual deaths from disease complications.
- Disseminated TB may occur in more than one-third of cases and the organs of the genitourinary (GU) tract are the second most common location of extrapulmonary TB worldwide.
- GU TB has a non-specific presentation and frequently mimics other more common GU pathology, which often delays diagnosis and results in progression to advanced disease.
- GU TB most frequently involves the kidneys, which become infected via haematogenous spread; common clinical findings include chronic dysuria, haematuria and persistent sterile pyuria; complications of GU TB may include chronic kidney disease, hypertension, chronic pain and infertility.
- Diagnostics: CT and intravenous pyelogram may demonstrate classic radiographical findings of GU TB, which include ureteral stricture, a dilated pelvic calyceal system, hydroureteronephrosis and bladder wall thickening. Sending three separate complete volume first void morning urine samples for acid-fact bacilli culture or nucleic acid amplification testing is the most sensitive diagnostic test and should be combined with imaging.
- Treatment of GU TB typically involves the same antibiotic regimen utilised for pulmonary infections, with attention to modifying treatment based on the drug resistance pattern of the TB strain isolated. Greater than 50% of cases will require surgery for reconstruction of a scarred collecting system, drainage of an abscess or hydronephrosis, or complete removal of an infiltrated kidney.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed

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