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Case report

Thoracoabdominal actinomycosis – Chameleon through kaleidoscope

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ABSTRACT

Actinomyces is a gram-positive anaerobic bacterium that generally inhabits the human commensal flora of the bronchial system, the gastrointestinal and urogenital tract. In the rare case of becoming invasive under certain circumstances, the resulting Actinomycosis affects most commonly cervicofacial, thoracic, abdominal and pelvic regions. Due to its rarity and presenting with nonspecific clinical symptoms, thoracic and/or abdominal Actinomycosis in particular are highly intriguing clinical conditions that can easily be mistaken for other diseases including malignancies. Astute considerations are therefore necessary whenever we are challenged diagnostically to allow early diagnosis and thus avoiding gratuitous invasive surgery. In order to highlight different issues of this ultimate chronic disease we report a particular case of thoracoabdominal Actinomycosis.

1. Introduction

The particularity of Actinomycosis is the diversity of its clinical presentation. Heavily summarized, (1) it may affect numerous organs of the human body, (2) it may present innumerable clinical symptoms and (3) it may resemble malignancy or a variety of other diseases [1,2]. In addition, its clinical occurrence is quite unusual and its scientific evidence is rather difficult, so it's no wonder that most clinicians are unaccustomed with this chronic infectious disease. From a microbiological point of view, Actinomycosis is caused by anaerobic or microaerophilic/capnophilic gram-positive bacteria that generally inhabit the human commensal flora of the bronchial system, the gastrointestinal and urogenital tract. In accordance with its population pattern, the most common clinical forms, inter alia, are the cervicofacial, thoracic, abdominal and pelvic [3,4]. The pathogenicity assumes damage on the mucosal membrane following dental or gastrointestinal tract procedures, aspiration, or digestive tract diseases [5]. The progressively invasive infection causes a gently continuing suppurative fibrosing inflammation, leading to florid abscess formation and chronic granulomatous lesions, developing draining sinus tracts that may discharge characteristic "sulfur granules", and directly disseminate via contiguous tissues [6]. Due to its peculiarities (its rarity, unspecific symptoms and tendency to perform as "surrounding mass invading structure"), Actinomycosis is at least at one point of its manifestation mistaken for a malignant tumor [3,4]. The featured case is a paradigm of the Actinomycosis' *art of metamorphosis*.

2. Case presentation

A 55-year old woman without significant past history presented in July with severe pain over left hemithorax and back. She had a boarding kennel and worked as horticulturist. She solely was a chronic smoker (30 pack years) and denied persistent cough, fevers, chills, hemoptysis, dyspnea, weight or appetite changes, sick contacts, or recent travel. A myocardial infarction could be ruled out with ECG and troponin within normal limits. The initiated cortisone and analgesic therapy alleviated the symptoms temporarily. Weeks later, the pain symptomatology returned in August. Due to the localization of the pain in conjunction with leukocytosis the general practitioner suspected urinary tract infection and consequently antibioticized the patient. Continuing pain intensity in September prompted thereupon inconclusive urologic examination. In October a rheumatic disease was suspected due to moderate increase of erythrocyte sedimentation rate and persistent leukocytosis - but prednisolone still wasn't a breakthrough. Meanwhile

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reached November, gynecological examination and esophagogastroduodenoscopy were normal. In December plasmocytoma was suspected - and was also ruled out hemato-oncologically. Finally, a CT-scan of the thoracoabdominal region performed in January revealed a peripherally enhancing fluid-attenuation within the left lower lobe of the lung, extending to the subdiaphragmatic space, reaching spleen and left kidney, and concluded at the site of a meanwhile newly formed skin swelling at the left flank (Fig. 1A). Following transfer of the patient to our medical center, thoracic and/or abdominal malignancy could be ruled out clearing way for groundbreaking suspicion of an infection. Laboratory findings at that point in time was showing mild leukocytosis (13.0 × 10^3/µl), increased C-reactive protein levels (123.3 mg/l),

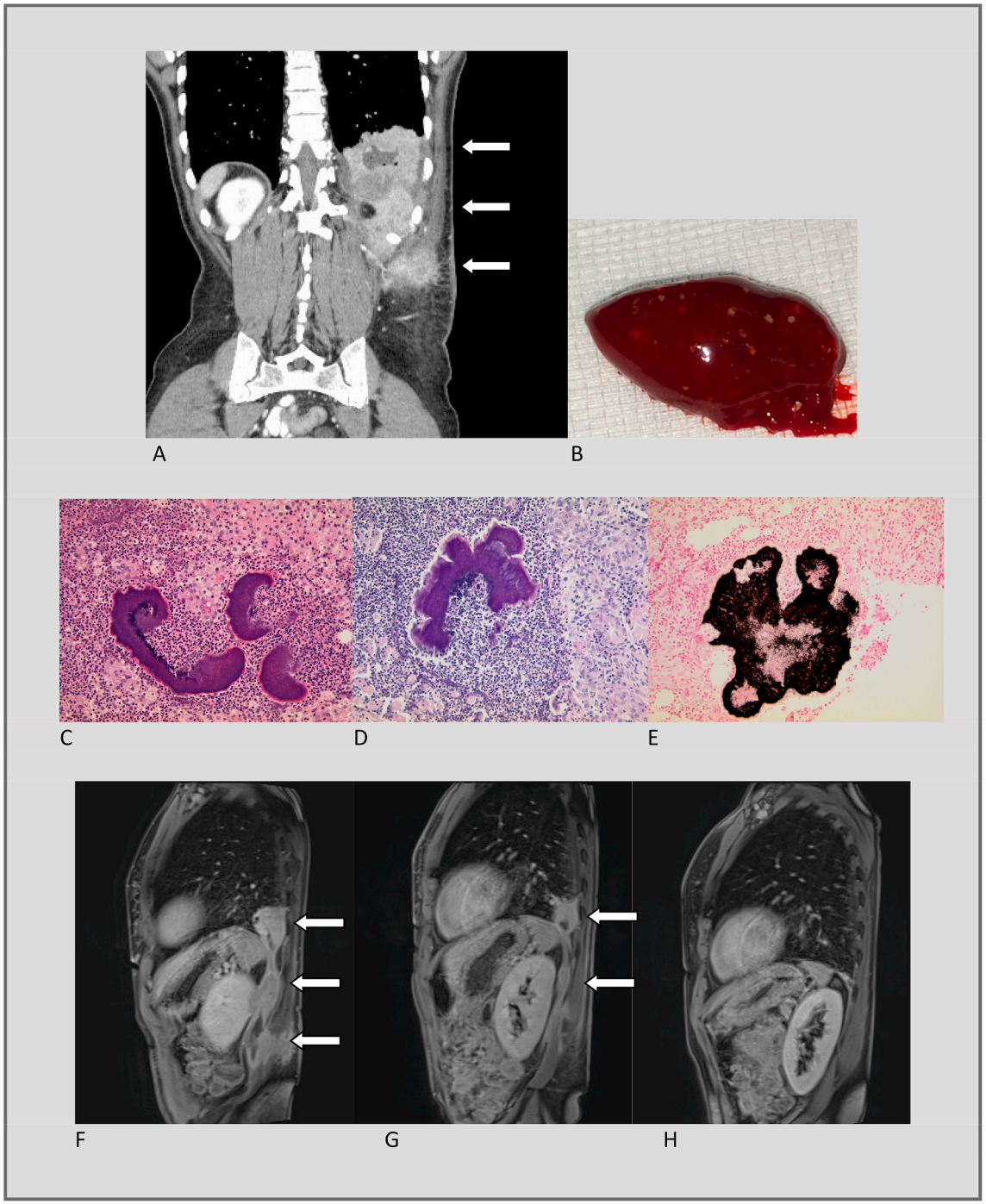

Fig. 1. A) Pre-therapeutic CT-scan revealing a peripherally enhanced fluid-attenuation within the left lower lobe of the lung, extending to the subdiaphragmatic space, reaching spleen and left kidney, and concluded at the left flank (arrows). B) Abscess drainage revealing purulent discharge with "sulfur granules". C) Histopathological examination I: Characteristic histological presentation of Actinomycosis with actinomycotic granules composed of radiating filaments with a dense granular core, surrounded by inflammatory cells composed of a mixture of neutrophils and eosinophils (hematoxylin and eosin (H&E) staining, magnification 100×). D) Histopathological examination II: Periodic Acid-Schiff (PAS) reaction confirms consistency with Actinomyces colonies ('sulfur granules'; magnification 100×). E) Histopathological examination III: A cluster of Actinomyces visualized by Grocott-Gomori Methenamine Silver stain (GMS; magnification 100×). F) Post-therapeutic MRI after one month (arrows indicating the lesion). G) Post-therapeutic MRI after three month (arrows indicating the shrinking lesion). H) Post-therapeutic MRI after six month (absent arrows reflecting the vanished lesion).

thrombocytosis (495 × 10^3/μl), and elevated erythrocyte sedimentation rate (80 mm/h). We consciously decided on an abscess incision at the swollen left flank only in order to avoid an unnecessarily outsized surgical procedure. The abscess drainage revealed a purulent discharge with sulfur granules (Fig. 1B). Histopathological examination demonstrated Actinomycosis-typical luminous strangles ubiquitously (Fig. 1C–E). Additionally initiated microbiological investigation (including intended 16S rRNA gene sequencing) remained negative in the meantime – in retrospect possibly as a consequence of either prolonged transport time to laboratory or storage in suboptimal media. As a result of the circumstantial evidence of Actinomycosis the patient was treated with high dose Penicillin G (intravenous therapy for 6 weeks, followed by 6 months of oral therapy). Follow-up examinations with a time range of one, three and six month showed a complete resolution of the lesion (Fig. 1F–H).

3. Discussion

Actinomycosis is typically being paraphrased by words like *rare*, *infrequent*, and *uncommon*. This is based on rather outdated epidemiological data, where the reported annual incidence was 1/300.000 persons - data dating as far back as the 1970s [7]. But there is still reason to believe that this data is more or less up-to-date. One reason for this is the global socioeconomic distribution pattern of the disease: due to a lack of knowledge about health issues and deprived access to qualified healthcare providers in developing countries and rural communities, the frequency of Actinomycosis is there tenfold higher than in highly-developed urban areas [8]. The risk factors remain the same during the past half century - only the longitude and latitude of its most frequent occurrence has changed. In simple terms, the impression of *rarity* and *infrequency* and *uncommonness* is linked to the socioeconomic environment in which he or she lives. And as human nature makes you think first of the most common than of the most infrequent (remember: hearing clippety-clop makes you rather think of horses than of zebras, and vice versa), Actinomycosis is hardly recognized at first sight, gaining him a *master of disguise* status.

In contrast to the rarity of its occurrence, the different aspects of Actinomycosis are widely investigated (Tables 1&2) [1–4]. In addition to this prosaic data we would like to highlight on some of the manifold aspects in a snapshot manner. The highest incidence rate meets middle-aged adults, with males slightly more often affected than women (3:1 ratio) [8,9]. Pre-existing conditions favor an increased susceptibility for an infection due to a weakening of the immune system [2,3,10,11]. The usual course of appearance of symptoms and correct diagnosis is ranged from one to twelve months [12]. In the present case we have to assume that the onset of the disease originates from the respiratory tract. The patient led - apart from being a nicotine addict - a healthy life and did not display any pulmonary Actinomycosis favoring conditions. Whether the living environment with intensified contacts to animals and plants in combination with the immunosuppressive property of smoking was beneficial to the development of the disease is rather vague and remains a matter of speculation.

From a microbiological view, the etiology of Actinomycosis is multilayered: (1) the etiological agents of the disease belong to various representatives of diverse genera (i.e. Actinomyces, Propionibacterium, and Bifidobacterium), and (2) usual actinomycotic lesions basically contain concomitant bacteria (of up to ten diverse bacterial species) [3,4]. These synergistic pathogens empower the moderate growth rate and virulence of the Actinomycetes and are primary accountable for the early symptoms of the disease. In this light renaming the term "Actinomycosis" (in the singular) into "Actinomycoses" (in the plural) seems to be highly appropriate and would accentuate the polyetiologic character of the disease instead of attributing to a single pathogen (but yet has to be determined by the microbiological community). Most commonly the diagnosis is made by histopathological examination of excised tissue, as it is more sensitive than culture alone, which remains sterile in more than 50% of cases [4,10,12]. Pathognomonic (but not exclusively proving) for Actinomycosis infection are sulfur granules, which are yellowish (or reddish to brownish) particles of up to 1 mm in diameter representing actinomycete microcolonies, concomitant bacteria and surrounding tissue reaction material enclosed by clubbed filaments and polymorphonuclear neutrophils [4,8,11]. The reason for frequent failure of culture is previous antibiotic therapy, inhibition of

Table 1
Clinical manifestations of Actinomycosis (selection of relevant information compiled from Refs. [1–4] without claim of completeness).

Cervicofacial	**~50% of all cases** Risk factors: poor oral hygiene, orofacial trauma, foreign bodies penetrating the mucosal barrier (bone splinters, fish bones or spicules of grass or grain), dental procedures, gingivitis, periodontal disease, chronic tonsillitis, otitis, mastoiditis, diabetes, immunosuppression, malnutrition, local tissue injuries by tumors, cervicofacial surgery, irradiation. Symptoms: painful, indurated cutaneous and soft tissue swelling ("woody" fibrosis), odontogenic abscess ("lumpy jaw syndrome"), draining sinus tracts with "sulfur granules", difficulties in chewing and chronic/relapsing course of the infection; most frequently affected tissue: mandible (~50%), cheek and chin (each ~15%).
Thoracic	**~15–20% of all cases** Risk factors: aspiration of oropharyngeal secretions, poor oral hygiene, neurologic and psychiatric diseases (e.g. seizure disorder), alcoholism, chronic lung disease (emphysema, chronic bronchitis, and bronchiectasis), diabetes mellitus, malnutrition, drug abuse, immunodeficiency (HIV-infection, steroid use, infliximab treatment, lung and renal transplantation), esophageal perforation, hematogenous dissemination. Symptoms: fever, cough, hemoptysis, chest wall pain, weight loss, sputum production, draining sinuses from the chest wall, dissemination to pleura, pericardium or chest wall, empyema & draining chest wall fistula(e).
Abdominopelvic	**~20% of all cases**; divided into gastrointestinal and pelvic disease
A) Gastrointestinal	Risk factors: abdominal operations, perforated acute appendicitis or colonic diverticulitis, mesenteric vascular insufficiency, ingestion of foreign bodies, caesarean sections or presence of prosthetic devices such as intrauterine device (IUD) contraceptives, frequently previous history of appendicitis. Symptoms: fever, abdominal pain, palpable mass, development of an external sinus, weight loss, nausea or vomiting.
B) Pelvic	Risk factors: prolonged use of IUD (>2 years, usually 7 years), vaginal pessaries or tampons, prolapse of the uterus, septic abortion, abdominal surgery, perforated appendicitis, tubo-ovarian abscesses and tumors. Symptoms: fever, pelvic pain, leucorrhea, menorrhagia, amenorrhea, malaise, weakness, weight loss.
Central Nervous System	Risk factors: hematogenous spread following thoracic or abdominal infections, direct dissemination of a cervicofacial lesion. Symptoms: headache, increased intracranial pressure, focal seizures, hemiparesis, aphasia, ataxia, abnormal reflexes; NOTE: linked to the highest mortality rate.
Other sites	**Bone and skin**: direct extension of adjacent soft tissue infection leading to periostitis, most frequently involved: mandible, ribs, and spine; risk factors: hematogenous spread of localized actinomycosis, contiguous spread of pulmonary actinomycosis, polymicrobial bone and joint infection following bone exposition (paraplegia and osteomyelitis of the ischial tuberosity). **Cutaneous**: wound contamination with saliva or dental plaque material (human bites or fist-fight trauma), immunosuppression (rheumatoid arthritis and psoriasis), immunosuppressive *anti*-TNF-α therapy, hematogenous spread. **Miscellanea**: vocal cord, middle ear, mastoid, urinary tract, orbita, muscle (i.e. M. psoas) and cardiac (i.e. pericardial) involvement.

Table 2
Synopsis of fundamental topics on Actinomycosis (rough summary of (1) causative agents, (2) virulence factors, (3) key elements for diagnosis [i.e. bacterial cultures and pathology], and (4) current treatment options; compiled from Refs. [1–4]; list does not claim to be exhaustive).

Causative agents	Actinomyces genus (family Actinomycetaceae, order Actinomycetales), including Arcanobacterium, Actinobaculum, Mobiluncus, Trueperella and Varibaculum with a dynamic genomic evolution of members of the family Actinomycetaceae. Infection can be associated with bacteria of different genera (Actinomyces, Propionibacterium, Corynebacterium, Mycobacterium, Nocardia and Bifidobacterium); in ≥98% of cases the causative agents are Actinomyces spp. >30 species of Actinomyces (A. israelii [median, ~73.3% of cases], A. naeslundii [median, ~7.0%], A. viscosus [median, ~4.8%], A. gerencseriae [median, ~2.0%], A. odontolyticus [median, ~1.4%], A. meyeri [median, ~1.0%], A. georgiae, A. neuii, A. pyogenes, and A. graevenitzii [<1.0% each]).
Virulence factors	Actinomyces has in general both a low growth rate and a low virulence capacity. Most relevant virulence factors: (1) fimbriae (property to bind collagen) and (2) porous biofilm production (impeding the antibiotic therapy of associated infections). Microbes belong in general to the indigenous microflora of human mucous membranes (e.g. bronchial system, gastrointestinal and urogenital tract). Local tissue ischemia (circulatory or vascular diseases, crush injuries, foreign bodies, or necrotizing capacity of simultaneously present additional microbes) is leading to infection spreading. Disease has endogenous origin, therefore neither liable to cause outbreaks nor to be transmitted among humans (except *punch actinomycoses* = human bites or fist-fight injuries).
Clinical specimen	The causative agent has to be isolated from a sterile body site (i.e. surgical biopsies: deep needle aspirates, pus, "sulfur granules" from draining sinuses, tissue biopsy specimens). Avoid swabs, urine, sputum or bronchial washing specimens.
Laboratory	Mild leukocytosis, increased C-reactive protein levels and erythrocyte sedimentation rate. Serological assays (i.e. serodiagnostic test to detect actinomycosis related antibodies) need to be improved. Molecular genotypic techniques: (1) 16S ribosomal RNA (rRNA) gene sequencing (standard method) (2) 16S ribosomal DNA restriction analysis (3) Real time Polymerase chain reaction (PCR) with specific primers (4) Fluorescence in situ hybridization (FISH) (5) Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry
Culture	⇧ test accuracy: (1) appropriate specimens (see above); (2) prompt notification of the laboratory; (3) rapid transport to the laboratory (process time ≤15 minutes); (4) prolonged culture on appropriate media. Culture mediums: chocolate blood agar, brain heart infusion broth, Brucella Blood Agar with hemin and vitamin K1. Use of semi-selective media (i.e. phenylethyl alcohol or mupirocin-metronidazole blood agar) inhibits overgrowth of concomitant organisms and hence increases isolation rates. Classical phenotypic tests (e.g. urease, catalase, fermentation of sugars) may lead to misidentification of species and genus.
Histopathology	Staining: Hematoxylin & Eosin (H&E), Gram stain, Periodic Acid-Schiff (PAS) reaction and Grocott-Gomori Methenamine Silver Stain (GMS). Complex of threads and club-shaped patterns, granulomatous border tissue containing fibroblasts, plasma cells, giant cells and polymorphonucleates. "Sulfur granules": basophilic central part and radiating border of eosinophilic clubs (H&E staining).
Treatment	(1) 2–6 weeks intravenous Penicillin G therapy (12–24 million U daily) followed by (2) 6–12 months oral penicillin V (or amoxicillin) therapy Alternative regimen: intravenous amoxicillin/ampicillin followed by oral amoxicillin. Alternative agents: amoxicillin/clavulanic acid, imipenem, ceftriaxone, chloramphenicol, erythromycin, doxycycline and clindamycin (in case of allergy or nonresponse to penicillin).

growth by concomitant and/or contaminant microorganisms, and poor methodology (i.e. inadequate culture conditions) [3]. As the members of the diverse genera are anaerobic to less stringently anaerobic to capnophilic or aerotolerant, culturing colonies of Actinomyces is challenging and time-consuming, requiring up to 14 days [2,3]. In order to sustain the histopathological pillar and hence to increase microbiological test accuracy special attention should be focused on (1) obtaining several clinically appropriate specimens (surgical biopsy or pus) to improve the detection of cultured bacteria, (2) giving a prompt notification of the laboratory about the clinical suspicion of Actinomycosis, (3) guaranteeing a rapid transport of the specimens to the laboratory and/or transport in an anaerobic transport medium (advised process time ≤15 minutes), and (4) ensuring a prolonged culture on an appropriate media in a proper atmosphere [4,8,13]. Even in our case the diagnosis is exclusively made by histopathological examination of excised tissue, whereas the attempt of cultivating the bacteria remained inconclusive, hence reinforcing the difficulty of its microbiological identification.

The fundamental principle for treatment of Actinomycosis is high-dose antibiotic therapy for a persistent period of time to ensure an adequate drug penetration into anyway poor perfused infected tissue and to prevent delayed relapse [4]. It is recommended to initiate intravenous therapy with penicillin G (typically 12–24 million U daily) for 2–6 weeks which is in case of clinical improvement followed by oral penicillin V (or amoxicillin) for at least 6–12 months [8,10,11,14]. The ideal duration of treatment remains vague because of the polymicrobial nature of the disease and the varying susceptibility in-between the Actinomyces species. Therefore the length of therapy has to be individualized and should be centered on the initial burden of disease and the intermediate response to treatment [3]. As prolonged antimicrobial therapy has the monopoly on treatment, surgery is solitary used in complicated cases or when percutaneous drainage or excisions for diagnostic purposes are indicated. We wisely did not decide to let the patient undergo surgery, in any form whatsoever, as we knew that drug treatment of the (at that moment) suspected disease would lead to *restitutio ad integrum* by itself.

Tracking down rare diseases is always challenging. The challenge to uncover Actinomycosis is elevated to a completely different level due to the complexity of its symptoms and versatility of its interdisciplinary disease patterns. On the background of this obscuring characteristic, Actinomycosis has already been named *a frequently forgotten disease* [4]. As from today's perspective we would like to propose an alternative transcription: *a commonly overlooked disease*. When we look at future prospects of different aspects of the disease, there are two sides of the same coin. On the one side there are high expectations placed on studies concerning (1) the current prevalence of Actinomycosis, (2) the role of immunosuppression as a supposed risk factor, (3) improvements of culture and instrumental techniques (e.g. MALDI-TOF, real-time PCR, and multiplex PCR), (4) advancements of present antibiotic treatment regimens, and (5) introduction of new treatment options (e.g. laser therapy and antibiofilm agents) [4]. On the other side the general low awareness of Actinomycosis remains unchanged. That is the crux of the present tense: despite pioneering improvements in many aspects of the disease, the key element to apply these enhancements - i.e. recognize the disease at an early stage - stays unaffectedly the same and delays a purposive treatment strategy. The mission is on us clinicians: adjusting the *myopia* towards Actinomycosis on a more appropriate level and hence increasing the likelihood of discovering a *chameleon through a kaleidoscope*.

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Declaration of competing interest

None.

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