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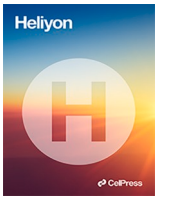

Case report

Nocardia farcinica brain abscess with torque teno virus co-infection: A case report

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ABSTRACT

Background: Brain abscesses caused by *Nocardia* are rare and difficult to diagnose. *Nocardia farcinica* is among the most common species; however, the conventional diagnosis of *N. farcinica* infection consists of cerebrospinal fluid (CSF) and blood culture and Gram staining. These procedures prolong the time to diagnosis and initiating treatment.

Case presentation: A 69-year-old woman with diabetes mellitus presented with headaches and dizziness persisting for 2 weeks, which was initially diagnosed as a brain abscess. Due to the unusual presentation and rapid progression of symptoms, she underwent surgical resection of the brain abscess. No pathogens were detected in blood or CSF cultures. However, metagenomic next-generation sequencing (mNGS) identified *N. farcinica* and Torque teno virus in pus extracted from the abscesses. The patient received appropriate antibiotic therapy and recovered fully without any residual neurological deficits.

Conclusion: mNGS useful for prompt diagnosis and selection of antibiotic therapy for brain abscesses caused by *Nocardia*. Surgical intervention is necessary in some cases.

1. Introduction

Brain abscesses, a clinical manifestation of central nervous system infection, are relatively rare and have a higher incidence in immunocompromised patients [1]. Nocardial brain abscesses account for only 2% of all intracranial abscesses [2]. Brain abscesses are the most common manifestation of nocardiosis in the central nervous system because of the unique tropism of *Nocardia* to the brain [3,4]. *Nocardia* usually infects the human body through the respiratory tract or skin contact. Central nervous system involvement is thought to be due to haematogenous spread or direct extension from an adjacent site of infection, or head trauma [5]. Although the development of imaging technology and new antibiotics has enabled the cure of brain abscesses, the mortality rate of nocardial brain abscess is as high as 30%, which is considerably higher than the 10% mortality rate in brain abscesses caused by other bacteria [6].

Nocardial brain abscess is a major public health threat due to its underdiagnosis and lack of adequate understanding. Conventional diagnosis of nocardial brain abscess still relies on isolation and identification of the organism from the infected site, which can take days to weeks, delaying patient treatment [7]. There is an urgent need for more rapid and precise diagnostic methods, enabling timely diagnosis and effective curative treatment. Metagenomic next-generation sequencing (mNGS) can identify pathogens in a variety of infectious diseases with high sensitivity and specificity and contribute to early and exact diagnosis [8]. Here, we report a case of a

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Nocardia farcinica brain abscess diagnosed by mNGS, discuss the methods of diagnosis and treatment, and review the literature.

2. Case presentation

A 69-year-old woman with a history of diabetes for more than 20 years was treated with oral hypoglycaemic agents (metformin and gliclazide) for more than 20 years. Here treatment was switched to repaglinide combined with insulin due to poor glycaemic control. She presented with a 2-week history of headaches and dizziness, with worsening of the symptoms over the past week. On examination, she had grade V muscle strength in the arms and legs, with normal muscle tone and no pathological signs detected. The clinical and laboratory findings are summarised in Table 1.

Contrast-enhanced magnetic resonance imaging (MRI) of the head revealed multiple irregular ring-enhancing lesions surrounded by extensive patches of oedema in the cerebral cortex (Fig. 1A–F). A brain abscess was considered as a possible diagnosis, although the presence of a metastatic tumour could not be ruled out. She was initiated on intravenous ceftriaxone combined with metronidazole for antibiosis, and intravenous mannitol to lower intracranial pressure, in addition to other symptomatic and supportive treatments. Her symptoms escalated, manifesting as nausea and vomiting, and progressing to clouding of consciousness and dysphoria. Consequently, we opted to perform a surgical procedure involving partial removal of the abscesses and right decompressive craniectomy under general anaesthesia. Throughout the operation, the intracranial pressure remained elevated, and the lesions exhibited resilient inflammatory hyperplasia tissue with abundant peripheral blood supply. The lesions were confirmed as brain abscesses containing white purulent tissue. The abscesses were excised, and the tissue was submitted for pathological examination, and the collected pus was preserved for further analysis. Postoperative computed tomography was performed to assess the patient's intracranial condition (Fig. 2).

Following surgery, the patient's consciousness gradually improved, although the patient exhibited somnolence and agitation. Empirical treatment was initiated with mannitol and vancomycin. Histopathology of the excised brain tissue revealed significant inflammatory cell infiltration, marked by localised tissue necrosis and concurrent abscess formation (Fig. 3). Bacteria were not detected in the culture and no fungi were isolated from the sample. mNGS identified the pathogen as *Nocardia farcinica* (Fig. 4A–B). The antibiotic regimen was changed to vancomycin and trimethoprim-sulfamethoxazole (TMP-SMX). When the patient's symptoms gradually improved, the antibiotic regimen was changed to oral TMP-SMX. Before discharge, MRI confirmed the successful removal of the lesions in the right temporal lobe, with no newly added lesions detected (Fig. 5A–C). Her condition was stable, the intracranial pressure returned to normal, and she was discharged from hospital. One week later, the patient visited the Shanghai HuaShan Hospital for follow up. During her hospitalisation, she commenced treatment with oral linezolid. Subsequently, the antibiotic regimen was modified to oral TMP-SMX supplemented by linezolid every 10 days.

This treatment regimen was continued for 12 months. After 6 months of antibiotic treatment, MRI revealed a noticeable reduction in the size of the intracranial lesion, with complete resolution of the surrounding oedema (Fig. 6A–C), and the patient remained asymptomatic without any neurological deficits. The timeline of the course of the patient's illness was shown in Fig. 7.

3. Discussion

Nocardia species are Gram-positive aerobic bacteria that are ubiquitous in soil, water, and decaying plant matter. *Nocardia* is an opportunistic pathogen that predominantly infects individuals with compromised immune systems. This susceptibility includes those undergoing immunosuppressive therapy, individuals with malignancies, human immunodeficiency virus (HIV) infection, diabetes mellitus, recipients of stem cell or solid organ transplants, individuals with chronic lung disease, or those undergoing prolonged corticosteroid therapy [9]. Within the spectrum of nocardiosis, *Nocardia asteroides*, *Nocardia basiliensis*, and *Nocardia farcinica* stand out as the most prevalent infectious agents [10]. Nocardial brain abscesses tend to occur in individuals aged over 60 years, and the age

Table 1
Clinical and Laboratory variables.

Laboratory variable	Measurements	Normal value	Clinical variable	Measurements
WBC (10^9/L)	8.4	3.5–9.5	GCS	14/15
NE# (10^9/L)	6.1	1.80–6.30	Temperature (°C)	36.4
MO# (10^9/L)	0.75	0.10–0.60	Blood pressure (mmHg)	139/82
LY# (10^9/L)	1.5	1.1–3.2	Respiratory rate	18
HGB (g/L)	136	115~150	Heart rate	76
hsCRP (mg/L)	18	0.0–5.0	KPS	70
Na (mmol/L)	134	137~147	VAS	6
K (mmol/L)	4.17	3.5–5.3		
PT (sec)	12.2	9.4–12.5		
PT-INR	1.13	0.90–1.20		
APTT (sec)	29.8	25.1–36.5		
HbA1c (%)	9.57	4.80–5.90		
GLU (mmol/L)	6.85	3.80–6.20		

WBC: white blood cell; NE, neutrophil; MO, monocyte; LY, lymhocyte; HGB, hemoglobin; hsCRP, high sensitivity C-reactive protein; PT, Prothrombin time; INR, International normalized ratio; APTT, Activated partial thromboplastin time; HbAlc, Glycosylated hemoglobin; GCS, Glasgow Coma Scale; KPS, Karnofsky Performance Scale; VAS, Visual analogue scale.

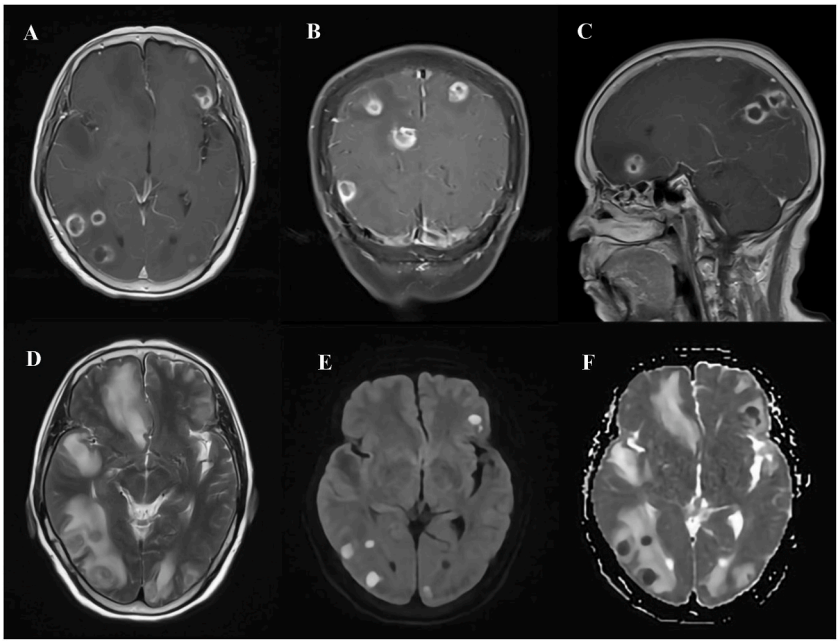


Fig. 1. Contrast-enhanced MRI scans of this case revealed multiple lesions in the right cerebral hemisphere with irregular ring enhancement: A (T1W transverse axis), B (T1W coronal), C (T1W sagittal), and D (T2W transverse); E, exhibited high signal intensity on DWI; F, demonstrated low ADC values.

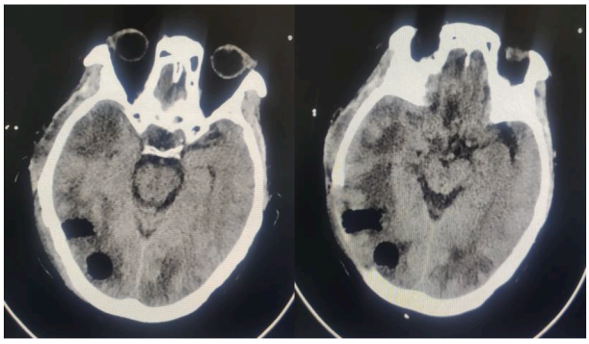


Fig. 2. Post-operation CT showed swelling and gas accumulation in the surgical area.

of our patient (69 years) is consistent with this epidemiology [11]. The higher incidence of nocardial brain abscesses in older adults may result from immunosenescence, partly due to the excessive production of proinflammatory cytokines by macrophages and fibroblasts which are critical for the development of nocardial brain abscess [12,13]. *Nocardia* has been labelled as a "great mimic" because of the diversity of its clinical presentation, and the clinical presentation of nocardial brain abscesses can be difficult to distinguish from primary brain tumours, metastases, and ischaemic stroke [14–17]. Notably, CT and conventional MRI are inadequate for distinguishing brain abscesses from other ring-enhancing lesions, particularly intracranial metastatic malignancies. Nevertheless, MRI remains the first choice for the diagnosis of suspected nocardial brain abscesses. Moreover, the location, size, and appearance of nocardial brain abscesses alone cannot be distinguished from other causes of bacterial abscesses. Therefore, in the early treatment, we use empirical antibiotics to treat the patient. During the course of treatment, the abscesses were excised as the patient's symptoms worsened, accompanied by a significant increase in intracranial pressure. In general, surgical aspiration is recommended as the first choice for lesions or abscesses larger than 2.5 cm in diameter that do not shrink within 4 weeks [18]. Capsule retention after abscess aspiration to be predisposes to recurrence. Hence, we opted for direct excision of the abscess. In addition, craniotomy and excision of the entire abscess and wall are generally considered more effective than aspiration and drainage [19–21]. Mamelak et al. [19] retrospectively reviewed 131 cases and reported an estimated a mortality rate of 24% after craniotomy and excision, 50% after aspiration or drainage; 33% in patients with a single abscess, and 66% in patients with multiple abscesses. Aspiration and drainage not only serve to confirm the diagnosis and select appropriate antimicrobial therapy, but are also crucial treatment modalities, especially in patients with comorbidities or surgically challenging lesions.

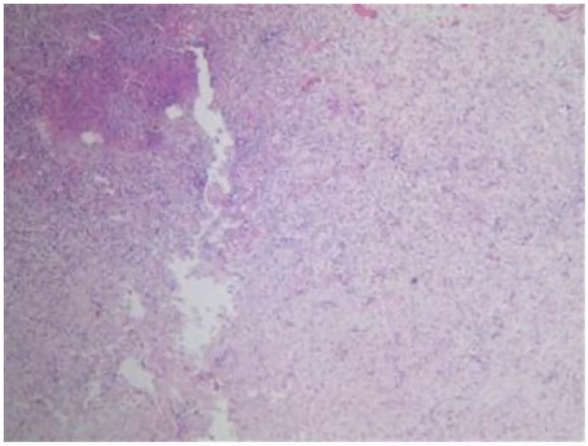


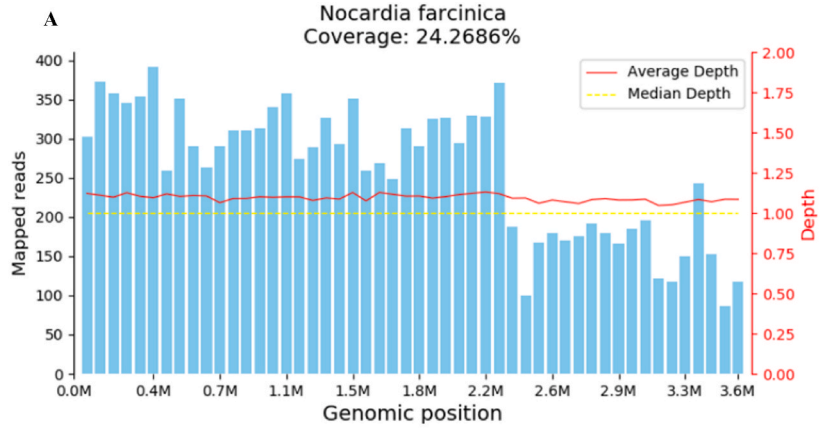
Fig. 3. Pathological picture report showed that acute and chronic inflammatory cell infiltration were massively seen in the tissue, with local tissue necrosis accompanied by abscess formation.

The most common method of diagnosing nocardial brain abscesses is bacterial culture. However, it generally takes approximately 7 days to obtain bacterial culture results, sometimes extending to over 2 weeks for slow-growing species [22]. This not only delays the diagnosis of the disease but also delays the initiation of targeted antibiotic treatment, thereby aggravating the difficulty of treatment. In this context, mNGS is able to identify a wide range of pathogens with high sensitivity and specificity. The application of this technology is useful for the early and accurate diagnosis of nocardial brain abscesses and enables timely initiation of targeted treatment strategies. In this case, the first workup, including blood and cerebrospinal fluid (CSF) culture, was negative for bacterial infection. We cannot rule out the presence of this condition, because early antibiotic treatment may reduce the detection rate. Hence, the timely diagnosis of *Nocardia farcinica* brain abscess complicated by Torque teno virus (TTV) infection was facilitated by mNGS detection, aligning with the prevailing trend for the diagnosis of *N. farcinica* infection in China, where it is the most frequently encountered *Nocardia* species [11]. The distribution of antimicrobial susceptibility varies widely among *Nocardia* species, but in general, only amikacin, linezolid, and TMP-SMX show high activity against most species [23,24]. Although TMP-SMX is the mainstay of antimicrobial therapy for nocardiosis, other antibiotics may be required because of sulfonamide allergy or antibiotic resistance. Linezolid is effective for the treatment of moderate-to-severe nocardiosis, showing 100% drug susceptibility in *Nocardia* species [25]. However, prolonged use of linezolid carries a heightened risk of haematological toxicity, and linezolid is also much more expensive and less widely available than most alternative antibiotics, constraining its clinical use [26]. Amikacin in isolation has limited use because of its inadequate penetration of infection sites, such as the central nervous system, and its associated toxicities. Imipenem, a β-lactam antibiotic, may serve as an alternative to TMP-SMX. Notably, the effectiveness of imipenem varies among different *Nocardia* species, with a study by Wang et al. [11] reporting a resistance rate of up to 40.5%. Consequently, our initial choice was TMP-SMX therapy, and considering the potential emergence of drug resistance, we subsequently opted for linezolid, which is known for its enhanced potency. Due to the risk of haematologic toxicity, linezolid was eventually replaced with TMP-SMX for 1 year, considering central nervous system involvement.

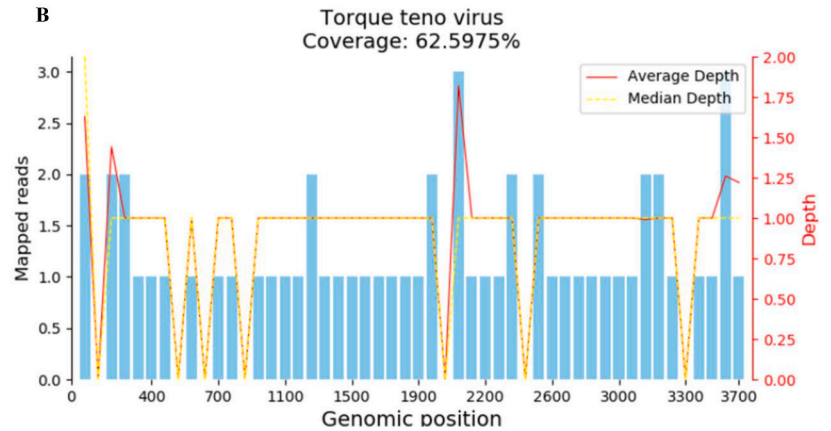
Notably, in this case, mNGS revealed the presence of TTV infection. TTV, single-stranded circular DNA viruses, are generally prevalent in the blood as human symbiotic viruses, which are present as chronic infections in more than 80% of the general population, thereby mediating viraemia [27,28]. mNGS has revealed that TTV is the most abundant eukaryotic virus in the human virome, with high variability [29]. Increasing evidence suggests that the level of TTV viraemia is highly correlated with the level of immunity of the infected host, especially in immunosuppressed populations such as patients undergoing solid organ transplantation, blood transfusion, cancer, or immunosuppressive therapy [30–32]. Based on this, TTV viraemia has been proposed as a biomarker of compromised immune system function [33]. Despite this, there is currently a lack of clear evidence linking TTV to human pathology, and current evidence suggests that the virus is a component of the normal human microbiota, and not a pathogen [29,34,35]. However, limited research has been conducted on the associations between TTV and brain diseases, especially in the CSF [36]. TTV may be associated with multiple sclerosis (MS); however, they have not been reported to be associated with neurological infections [37]. Regarding the TTV detected in the CSF in this case, the CSF may have been contaminated by blood during the collection process; or alternatively TTV may have been present in the CSF but had no influence on the disease, because it is generally considered non-pathogenic [38]. It is, however, not possible to rule out the possibility that TTV is a predictor of certain neurological diseases. The role of TTV in the nervous system warrants further study.

4. Conclusion

In summary, nocardial brain abscess is difficult to diagnose and is associated with high mortality. The use of mNGS greatly shortens the time to diagnosis of nocardial brain abscess. This not only allows doctors to formulate the best and most precise treatment strategy for the disease, but earlier diagnosis and initiation of treatment is likely to result in better prognosis.



Genus				Species		
Type	Generic name	Relative abundance	Sequence number	Species name	Confidence	Sequence number
G⁺	*Nocardia*	99.8%	20,974	*Nocardia farcinica*	99%	17,041



Species	Confidence	Sequence number
Torque teno virus	99%	25

Fig. 4. Metagenomic next-generation sequencing (mNGS) results of this case: A. Coverage of Nocardia farcinica was 24.27%. B. Coverage of Torque teno virus was 62.60%.

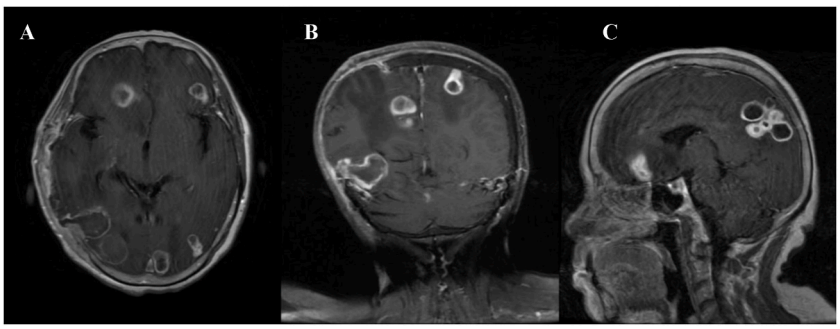


Fig. 5. Follow-up contrast-enhanced MRI before dischargement, A (T1W transverse axis), B (T1W coronal) and C (T1W sagittal) showed the meninges surrounded by the surgical areas were thickened and enhanced, and the lesions further shrinking in size compared with those in the previous film, no newly additional lesions were found.

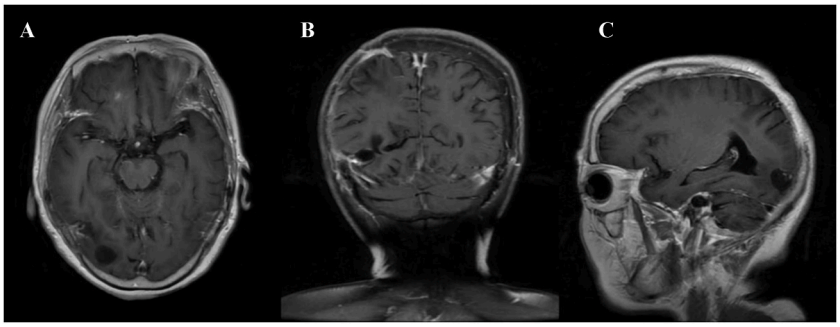


Fig. 6. Follow-up contrast-enhanced MRI at 6 months, A (T1W transverse axis), B (T1W coronal) and C (T1W sagittal) showed substantial resolution of the lesions and surrounded oedema.

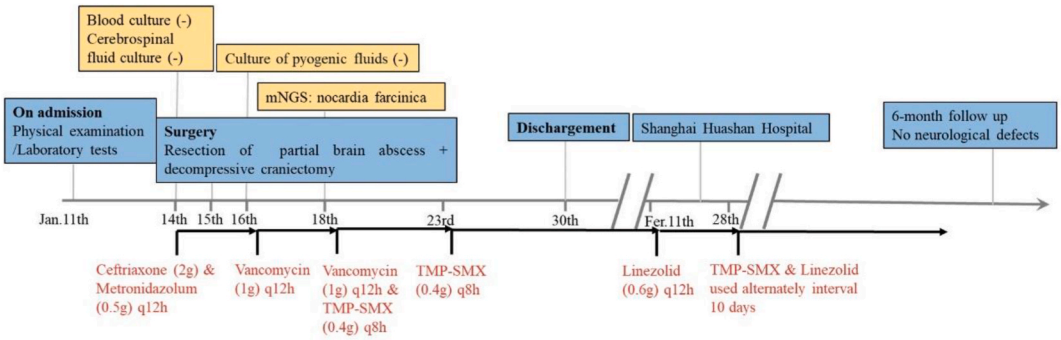


Fig. 7. Timeline of the treatment of this case.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University.

Consent for publication

The patient gave written consent for the publication of her anonymised case details and the associated images. A copy of the written consent form is available for review by the journal editor.

Availability of data and material

The datasets produced and analysed during this research are available from the corresponding author on reasonable request. The metagenomic sequence data associated with this article is accessible on the figshare database (https://figshare.com/) under the identification number 10.6084/m9.figshare.25358959.

CRediT authorship contribution statement

Yuting Gu: Writing – original draft. **Zide Wang:** Data curation. **Xiaohua Xia:** Writing – review & editing. **Guang Zhao:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CSF	cerebrospinal fluid
mNGS	metagenomic next-generation sequencing
MRI	magnetic resonance imaging
MS	multiple sclerosis
TMP-SMX	trimethoprim-sulfamethoxazole
TTV	Torque teno virus

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