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CASE REPORT

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Clinical and pathological features of cerebrospinal meningitis caused by *Pantoea agglomerans* : a case report

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Abstract

Background *Pantoea agglomerans* (*P. agglomerans*) is a gram-negative bacterium that is commonly isolated from plant surfaces, seeds, and the environment. As an opportunistic pathogen, it can cause blood, urinary and soft tissue infections in immunocompromised patients. In central nervous system, *P. agglomerans* infection has been report in children and immune-compromised patients, however, infection by such bacterium in nontraumatized immune competent adults has not been reported. Here, we report a case of *P. agglomerans* cerebrospinal meningitis accompanied by positive anti-myeloperoxidase (MPO) antibody in a 49-year-old female who has a history of black fungus planting.

Case presentation The patient manifested with repeated fever, headache, generalized muscle pain, and neurological defects. Cerebrospinal fluid (CSF) tests revealed a moderately elevated number of polymorphonuclear leukocytes (50–193 × 10^6/L), low glucose levels (0.54–2.44 mmo1/L), and extremely high protein content (2.42–25.42 g/L). Blood tests showed positive anti-myeloperoxidase antibodies lasting for 1.5 year before turning negative. Spine MRI showed thickening and enhancement of the whole spinal meninges. CSF metagenomic next-generation sequencing (mNGS) revealed 75,189 specific DNA reads of *P. agglomerans*. The patient underwent spinal laminectomy due to meningeal adhesions. Pathological results revealed fibrous tissue proliferation, inflammatory infiltration with focal necrosis and calcification in the dura mater. The patient was successfully treated with sufficient antibiotics at 1-year follow-up.

Conclusions People should be alert to CNS infections caused by *P. agglomerans* which presented with relatively mild clinical symptoms at onset, especially for those who contucts relevant agricultural and forestry work. The CSF characterization of *P. agglomerans* meningitis is elevated multiple nuclei white blood cells, significantly reduced glucose content, and markedly increased protein level which may be related to the secondary spinal membrane adhesions.

Keywords *Pantoea agglomerans*, central nervous system, Cerebrospinal meningitis, Metagenomic next-generation sequencing, MPO-ANCA

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Background

Pantoea agglomerans is a gram-negative bacillus that can cause disease in both humans and plants [1]. In humans, it is considered an opportunistic pathogen, with infections typically resulting from exposure to plant materials that penetrate the skin, a risk that is particularly high among individuals engaged in agriculture or horticulture [2, 3]. *P. agglomerans* infection can also be caused by contaminated intravenous fluids or iatrogenic sources and is more commonly observed in immunocompromised patients. Bloodstream infection caused by *P. agglomerans* can lead to end-organ infection, such as septic arthritis, synovitis, endophthalmitis, osteomyelitis, and endocarditis [1]. *P. agglomerans* has been recognized to be an opportunistic pathogen of meningitis in children and immune-compromised patients [4]. However, central nervous system infection by *P. agglomerans* in non-traumatized immune competent adults has not been reported to date.

Case presentation

A 49-year-old female was admitted to Shandong Provincial Hospital affiliated with Shandong First Medical University on January 12th, 2022, with a complaint of intermittent fever (highest temperature of 39.2 ℃), headache and generalized muscle pain for over one month. Figure 1 shows the baseline information about the patient. She visited a local neurological clinic before admission, and a blood test showed an elevated white blood cell count (WBC, 10.35×10^9/L; normal range: $4–9\times10^9$/L), elevated platelet count (492×10^9/L; normal range: $100–300\times10^9$/L), C-reactive protein (CRP) of 90.2 mg/L (normal range: 0-8 mg/L), and erythrocyte sedimentation rate of 99–123 mm/h (normal range: 0–20 mm/h). Infection-related tests, including the tuberculosis antibody test, T-SPOT test, *Mycoplasma pneumoniae* antibody, *Brucella* agglutination test, TORCH, and human cytomegalovirus (CMV) DNA quantification, were all negative. Autoimmune antibody tests showed antinuclear antibody (ANA) of 1:100 (normal range: <1:100), antineutrophil cytoplasmic antibody (MPO) of 280 RU/mL (normal range: 0–20 RU/mL), and positive (1:10; normal range: <1:10) perinuclear antineutrophil cytoplasmic antibody (pANCA). The first lumbar puncture was performed on day 20 from symptom onset, revealing an intracranial pressure of 95 mmH_2O (normal range:80-180mmH_2O), with 50×10^6/L (normal range:$0–8\times10^6$/L) nucleated cells (95% were multinucleate cells; normal range: <6%). The cerebrospinal fluid (CSF) glucose level was 2.4 mmol/L (normal range: 2.5-4.5mmol/L), and the protein level was 2.44 g/L (normal range: 0.15–0.45 g/L). Acid-fast bacillus smear, fungal smear, and cryptococcal capsule antigen test of CSF were all negative. Empirical anti-infectious treatment was given with acyclovir 0.5, q8h and ceftriaxone 2 g, q12h for 10 days, and vancomycin 1.0, q12h for 2 days. No significant relief in symptoms was noticed. CSF reinspection revealed a pressure of 99 mmH_2O, light yellow color, WBC of 130×10^6/L (multinucleate cells of

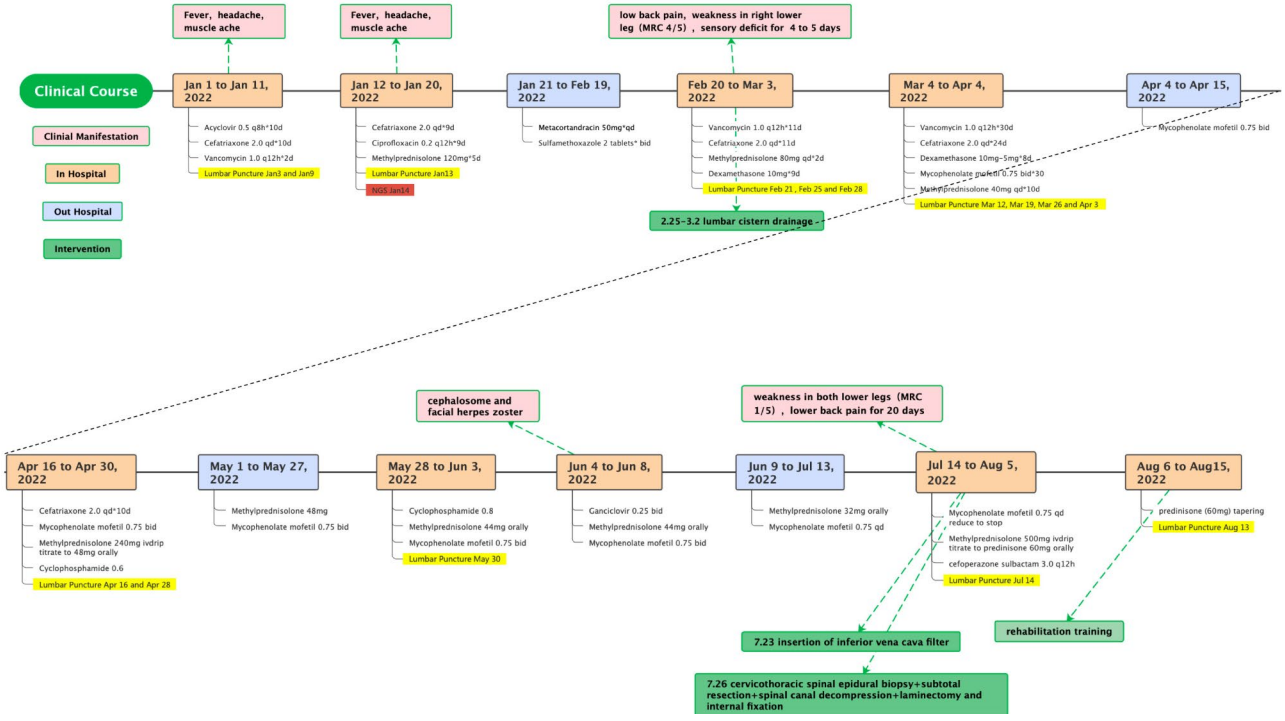

Fig. 1 The baseline information of the patient

42%), glucose of 1.21 mmo1/L, adenosine deaminase of 14.2 (normal range: 0–8) U/L, and protein of 9.95 g/L. The cranial magnetic resonance imaging (MRI) enhancement MRI and magnetic resonance venography (MRV) examinations 20 days after symptom onset showed no abnormalities in the brain parenchyma. Chest CT showed bronchial dilation and inflammation in the left upper lobe, chronic inflammation in both lungs, inflammatory nodules in the left upper lobe and right middle lobe, and small lymph nodes in the mediastinum and right heart diaphragmatic angle.

The patient had been cultivating black fungus for the past 3 years and had a history of hypertension for 10 years. She has not been to the epidemic area. Neurological physical examination on admission revealed no significant signs. Blood tests showed elevated WBC (11.61×10^9/L), elevated platelets (916×10^9/L), and elevated D-dimer (1.31 mg/L; normal range :0-0.5 mg/L). Quantitative testing for anti-nuclear and anti-neutrophil cytoplasmic antibodies showed ANA 1:1000 (+), pANCA 1:10 (+), MPO 4.4 (normal range:0–1 CU), anti-proteinase 3 antibodies (PR3) 1.5 (normal range: 0–20 CU), and anti-elastase antibodies 5.74 (normal range: 0-1CU). Tests for anti-phospholipid antibodies and lupus anticoagulants were normal. MPO and p-ANCA antibodies turned negative after one and a half years in July 2022. Inflammatory markers showed elevated cytokines: interleukin-6 (IL-6) 12.89 (normal range: 0-5.4pg/ml), interleukin-5 (IL-5) 19.29 (normal range: 0-3.1 pg/ml), interferon-α 10.93 (normal range: 0-8.5pg/ml), CRP 30.8 mg/L, and ESR 89 mm/h. Lumbar puncture showed a pressure of 125 mmH_2O and nucleated cells of 193×10^6/L (multiple nuclear cells of 36%), glucose 1.56 mmol/L, chloride 112 (normal range: 120–135 mmol/L), protein 3.91 g/L, Epstein–Barr virus (EBV), CMV, and *Mycobacterium tuberculosis* DNA were negative. Cellular immune function-associated factors, including total T cells, T helper cells, NK cells, and total B cells, were within normal ranges. CSF mNGS detected 75,189 specific reads of *P. agglomerans* in CSF, with a genome coverage of 68.59% (Fig. 2). CNS infection caused by *P. agglomerans* was considered. Ciprofloxacin 0.2 g q12h, ceftriaxone 2.0 g, qd, and methylprednisolone 120 mg with sequential tapering were given. The patient showed signs of improvement after one week of treatment, becoming afebrile and without headaches on the day of discharge. At the outpatient clinic, the patient was prescribed compound sulfamethoxazole (2 tablets twice daily) and acetic acid prednisone (50 mg once daily) as sequential treatment. However, after stopping the antibiotics, the patient experienced fever and headaches again and was readmitted to the hospital due to sudden onset of lower back pain, numbness, and weakness in both lower limbs. Upon admission, neurological examination revealed decreased muscle strength (grade 4) and active tendon reflexes in both lower limbs, decreased superficial sensation below the Thorax 10 plane, bilateral Babinski signs (+), and no signs of meningeal irritation (-).

Repeated lumbar puncture showed a pressure of 200 mmH_2O, nucleated cells of 193×10^6/L, chloride of 113.8 mmol/L, glucose of 1.90 mmol/L, and protein of 25.42 g/L in CSF. Enhanced MRI of the brain and thoracic and lumbar spinal cord showed varying degrees of thickening and enhancement of the meninges in the cervical, thoracic, lumbar and sacral spine, indicating spinal meningitis (Fig. 3a, b, c), Antibiotics (vancomycin 1 g q12h for 11 days, followed by ciprofloxacin 2 g/d for 11 days) and glucocorticoids (methylprednisolone 80 mg/d for 2 days and dexamethasone 10 mg/d for 9 days) were given.

On February 25th, lumbar puncture was performed with a pressure of 120 mmH_2O. CSF examination showed nucleated cells of 80×10^6/L, chloride of 118.0 mmol/L, and glucose of 5.92 g/L. CSF biochemical tests on February 28th showed a chloride level of 117.0 mmol/L, glucose level of 0.54 mmol/L, and protein level of 6.48 g/L. Routine CSF analysis revealed a turbid appearance, nucleated cell count of 233×10^6/L, and red blood cell count of $27{,}000\times10^6$/L. On February 20th, for two days. cephalosporin 0.75 g bid. The patient was discharged on March 3rd, 2022 and was transferred to a local hospital for further treatment with ceftriaxone, vancomycin, methylprednisolone 40 mg, and secapin 0.75 g bid. Considering that antineutrophil cytoplasmic autoantibody (ANCA)-related vasculitis could not be ruled out, two injections of cyclophosphamide were given on April 16th and May 28th, 2022, with doses of 0.6 g and 0.8 g, respectively. The patient occasionally experienced mild headaches and fever but no further lower back pain, and the strength in the lower limbs improved.

On June 8th, 2022, the patient presented with herpes zoster on the head and face and was treated with acyclovir 0.25 mg bid at the local hospital. On June 24th, the patient complained of back pain and weakness in both legs. On July 12th, the weakness in both legs worsened with a muscle strength of grade 1. On July 14th, the patient was admitted to Qilu Hospital. Spinal MR showed thickening of the meninges ranging from the C6 to T10 level (Fig. 3d, e, f). On July 15th, the patient had a PR3 level of 1.08 (normal range 0–1 U/mL) and an anti-neutrophil cytoplasmic antibody (MPO) level of 3.12 (normal range 0–1 U/mL). The patient was treated with levofloxacin 0.5 mg qd and cefoperazone sulbactam 3.0 g q12h for four days, as well as methylprednisolone 500 mg pulse therapy (gradual reduction) and a gradual reduction and discontinuation of celecoxib. On July 26th, the patient underwent cervical and thoracic laminectomy, partial removal, decompression, and internal fixation of the vertebral plate. The pathological results showed

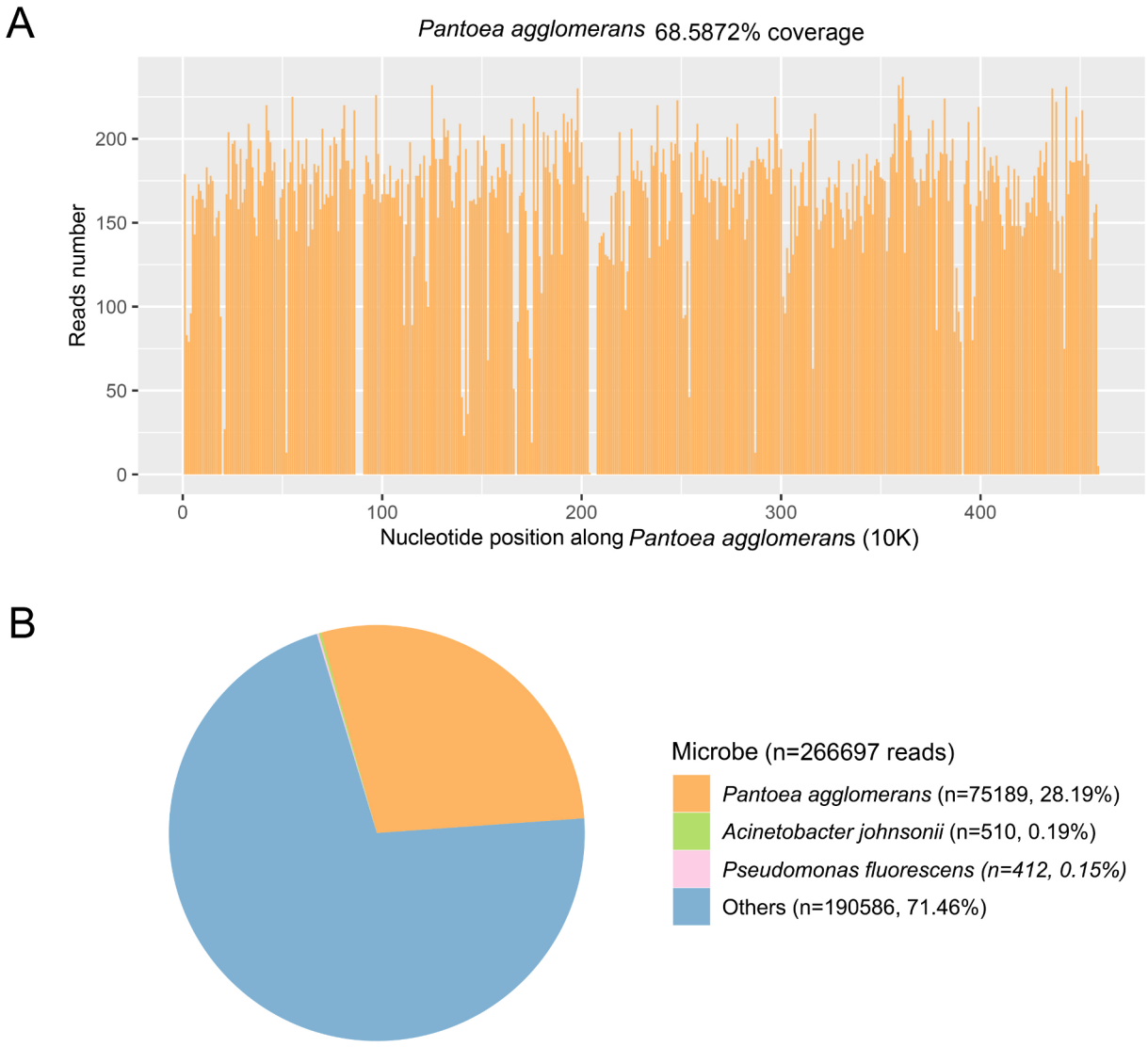

Fig. 2 CSF mNGS detection on January 14th, 2022. The coverage and detected specific read number of *P. agglomerans* are shown in **A** and **B**, respectively. A total of 75,189 specific reads of *P. agglomerans* were detected in CSF, with a genome coverage of 68.59%

fibrous tissue proliferation in the dura mater, with a large amount of inflammatory cell infiltration and focal necrosis and calcification in the dura mater and surrounding connective tissue (Fig. 4). The patient underwent several lumbar punctures (Table 1). On August 6th, 2022, after rehabilitation training in the local hospital, the patient's lower limb strength improved, and the patient was able to stand with support. Follow-up visits on February 15th, 2023, revealed that the patient occasionally experienced a fever with a body temperature of approximately 37.5 ℃, and the prednisone dosage had been reduced to 7.5 mg.

Discussion and conclusions

P. agglomerans infection is more likely to occur in immunocompromised patients, with few reports in otherwise healthy individuals [5]. *P. agglomerans* infection in the CNS has been reported in some cases, the majority of which either had experienced a neurological insult and/or had undergone an invasive neurological procedure [6, 7]. However, the patient in the present case report had no immunodeficiency-related diseases and denied a history of injury. To our knowledge, there are no reports of healthy adults developing *P. agglomerans* infections in the CNS, therefore, this case report would be important for clinical practice and help clinicians recognizing for such infectious disease at earlier stage.

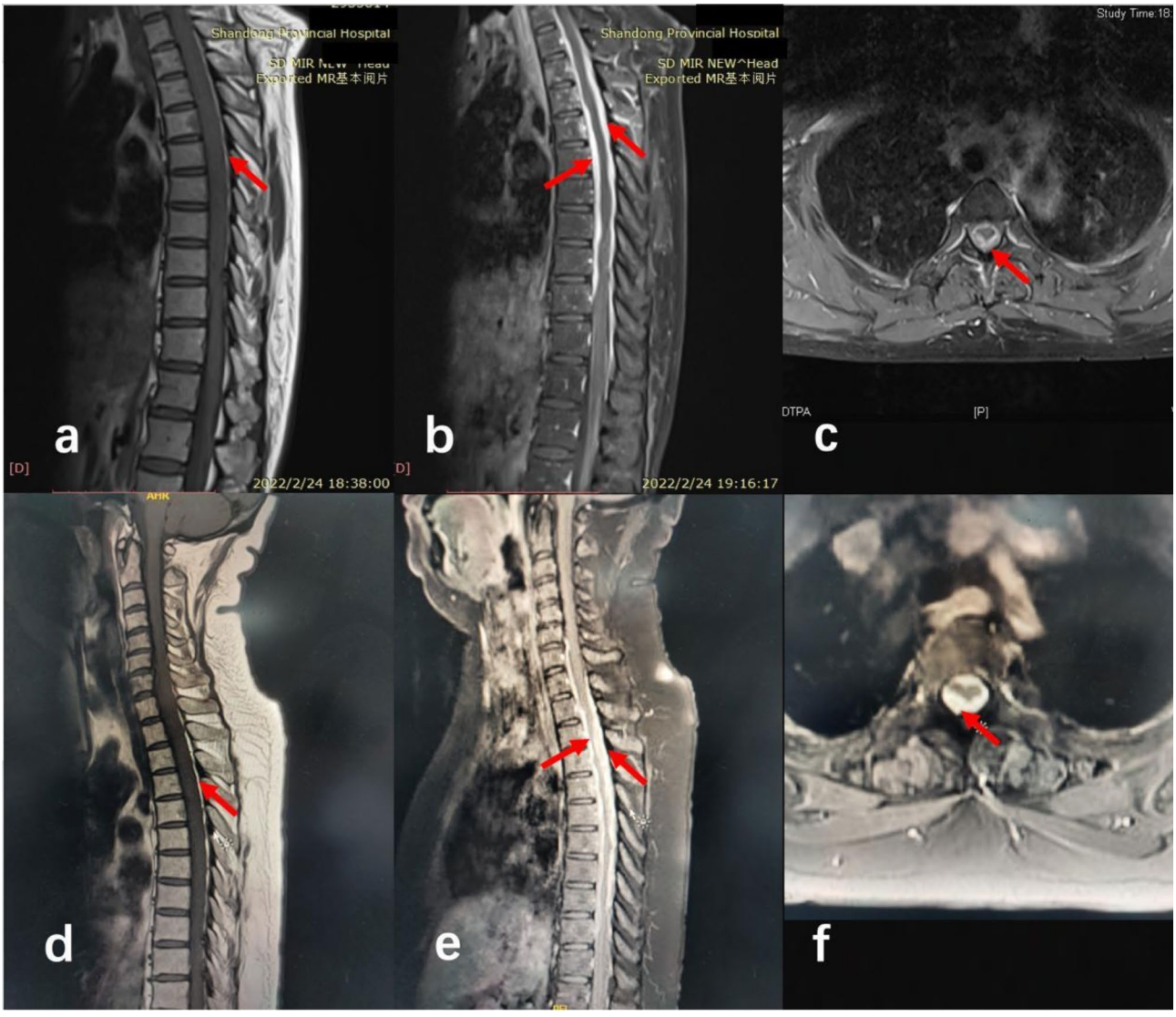

Fig. 3 Thoracic spinal MRI on February 24th, 2022 and July 19th, 2022. On February 24, 2022, the patient's thoracic spinal MRI revealed thickening **(a)** and enhancement **(b)** of the spinal meninges, as well as compression **(c)** of the spinal cord at the C7-T10 level. A cervical and thoracic spinal MRI conducted on July 19, 2022, showed thickening **(d)** and significant enhancement **(e)** of the spinal meninges, a narrow spinal canal, and compression **(f)** of the spinal cord at the C6-T10 level

Research has suggested that severe *P. agglomerans* infections may become more frequent in agricultural population growing [8]. This patient worked in a black fungus cultivation shed for three years, and it is speculated that frequent exposure to the pathogen during work may have been the cause of infection. Although there have been reports of *P. agglomerans* infections in the lungs or bloodstream of healthy patients, the relationship between the chronic pulmonary inflammation revealed by chest CT and the *P. agglomerans* CNS infection of this patient remains unclear.

In most cases, the clinical symptoms of *P. agglomerans* infections are mild, and patients can completely recover with appropriate antibiotic treatment [9, 10]. In the initial stage of infection in this case, the clinical symptoms were also mild, and there were no positive neurological signs or abnormalities on cranial imaging. The prolonged course of the patient's illness may be due to the inability of antibiotics to cross the blood–brain barrier and the irregular antibiotic treatment course. The significant increase in protein levels in CSF can cause arachnoid adhesions and spinal cord injury. The inflammation results in nerve root edema and hyperemia, leading to fibrinous exudate. CSF carries and dilutes phagocyte and fibrinolytic enzymes, forming fibrinous bands and resulting in the arachnoid adhesions eventually [11]. Timely, adequate, standardized, and effective antibiotic treatment

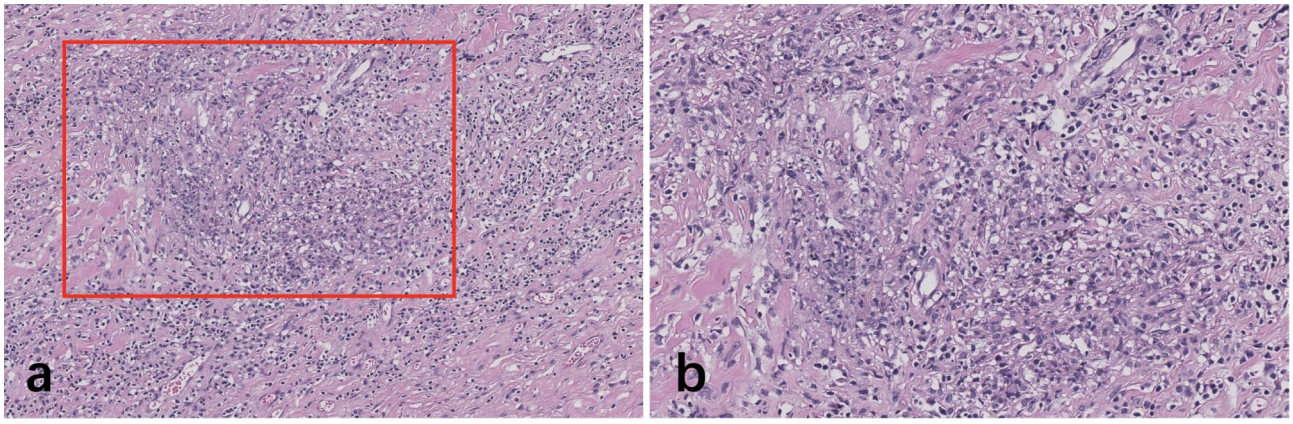

Fig. 4 The pathological results showed fibrous tissue proliferation in the dura mater, with a large amount of inflammatory cell infiltration and calcification in the dura mater and surrounding connective tissue

Table 1 CSF test results of this patient

Date	Pressure (mmH_2O)	Cell count (10^6)	Multinucleate cells percentage	Mononuclear cells percentage	Protein (g/L)	Chloride (mmol/L)	Glucose (mmol/L)
01/03/2022	95	50	95%	5%	2.44	NA	NA
01/09/2022	99	130	42%	58%	9.95	NA	1.21
01/13/2022	125	193	36%	64%	3.91	112	1.56
02/21/2022	200	193	50%	50%	25.42	113.8	1.9
02/25/2022	120	80	22.5%	77.5%	5.92	118	2.44
02/28/2022	NA	233	36%	64%	6.48	117	0.54
03/12/2022	160	135	15%	85%	0.8	116	2.27
03/19/2022	135	50	65%	35%	4.31	115	2.04
03/26/2022	180	20	40%	60%	3.65	120	1.69
04/03/2022	100	4	NA	NA	1.82	124	2.14
04/16/2022	200	40	NA	NA	8.04	NA	NA
04/28/2022	210	23	NA	NA	0.88	NA	NA
05/30/2022	265	6	NA	NA	1.14	NA	NA
07/14/2022	220	70	NA	NA	10.03	97	1.98
08/13/2022	NA	30	NA	NA	NA	NA	NA

and lumbar puncture drainage may be beneficial in preventing this complication.

The CSF in this case showed moderate cell count elevation mainly composed of multiple nuclei, significantly reduced glucose content, and markedly increased protein levels. The glucose level of CSF in *P. agglomerans* CNS infection is similar to that of tuberculous meningitis, but the chloride level, significantly increased protein content, or level? and milder clinical manifestations are different from tuberculous meningitis, which can be used to distinguish the two diseases. The cerebrospinal fluid cytology in our patient presented with mixed granulolymphomonocytic features which is usually seen in late phases of successfully treated purulent meningitis [11]. The fluctuation in cell counts during the disease may related to treatment or disease progression, the processing of CSF samples and testing methods in different hospitals.

In this case, inflammatory markers (ESR, CRP, IL-6) and platelets were significantly elevated, and ANA, MPO, and elastase antibodies were positive. Inflammation is a cause of thrombocytosis [12], and IL-6 is a key mediator in this process [13]. Thus, the significant increase in IL-6 and platelets in this case might be due to an exaggerated inflammatory response triggered by infection. On the other hand, the positivity of MPO-ANCA antibody in infectious diseases has been frequently reported [14–16]. The possible reasons for this phenomenon were as follows: (1) Patients who have ANCA-associated vasculitis with positive MPO-ANCA antibodies are prone to infection during the course of the disease. Studies have shown that infection is a critical cause of death in MPO-ANCA antibody-positive ANCA-associated vasculitis patients [17]. The incidence of opportunistic infections caused by rare pathogens has been reported to increase annually in these patients [18]. (2) Infections are also verified to be a cause of ANCA-associated vasculitis with

positive MPO-ANCA antibody. A systematic review of 23 cases showed a median of 3 months between infection and the development of vasculitis, among which 52.2% of patients experienced vasculitis regression after infection relief [19]. Furthermore, previous studies revealed that ANCA-associated vasculitis patients were more likely to exhibit pulmonary and neurological manifestations, while patients caused by infections more frequently had dual ANCAs (high PR3, low MPO), aCLs, β-GP I, cryoglobulins, and hypocomplementemia [20]. In this case, the patient did not have multiple serological abnormalities in vasculitis antibodies other than MPO-ANCA antibody. In addition, no crucial clinical manifestations of vasculitis were observed in this patient. More importantly, MPO-ANCA antibody quickly turned negative in July 2022. Hence, MPO-ANCA antibody positivity might be a change secondary to *P. agglomerans* infection in this case.

The genus *Pantoea* is anaerobic. Routine CSF cultures do not always cover anaerobic bacteria due to the low incidence of infection in the CNS. Furthermore, anaerobic culture is influenced by many factors. Culturing anaerobic gut bacteria in vitro is a great challenge, requiring the use of specialized techniques and equipment to ensure that all oxygen is removed from the system during in vitro culture [21]. In this case report, *P. agglomerans* was not detected by CSF anaerobic culture or the first mNGS. Subsequently, massive unique *P. agglomerans* DNA reads were detected by the second mNGS, indicating *P. agglomerans* infection. This indicates that mNGS has advantages in the diagnosis of *P. agglomerans* infection in the CNS.

In conclusion, doctors should be alert to *P. agglomerans* infections, especially for those with relevant agricultural and forestry work. CNS infections caused by *P. agglomerans* have relatively mild clinical symptoms, with multiple nuclei elevation, significantly reduced glucose content, and markedly increased protein levels in the CSF. The increased protein levels may cause secondary spinal membrane adhesions and other damage. mNGS has advantages in the diagnosis of CNS *P. agglomerans* infection. Early and sufficient antibiotic treatment and drainage may be beneficial for the patients.

Abbreviations

MPO	Positive anti-myeloperoxidase
P. agglomerans	Pantoea agglomerans
CSF	Cerebrospinal fluid
mNGS	metagenomic Next-generation sequencing
CRP	C-reactive protein
CMV	Cytomegalovirus
ANA	Antinuclear antibody
pANCA	Perinuclear antineutrophil cytoplasmic antibody
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
PR3	anti-proteinase 3 antibodies
EBV	Epstein–Barr virus
IL	Interleulin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10035-6.

Supplementary Material 1

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Author contributions
HHL and ZLZ were involved in the clinical care of the patient. HHL, CCL and ZLZ designed the case report, created figures, and drafted the manuscript. YZ and HX reviewed the manuscript. SGG and JY contributed to the revision of the manuscript and led the scientific discussion. All the authors have read and approved the final manuscript.

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Data availability
Sequence data that support the findings of this study have been deposited in the SAR repository with the primary accession code PRJNA1113875 (persistent web link: https://submit.ncbi.nlm.nih.gov/subs/sra/SUB14444634/overview).

Declarations

Ethics statement and consent to participate
The studies involving human participants were reviewed and approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) and minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Competing interests
The authors declare no competing interests.

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