

DOI: 10.4274/mjima.galenos.2019.2019.24  
Mediterr J Infect Microb Antimicrob 2019;8:24  
Erişim: <http://dx.doi.org/10.4274/mjima.galenos.2019.2019.24>

# Idiopathic CD4 Lymphocytopenia (HIV-Negative AIDS): Case Report and Literature Review

İdiyopatik CD4 Lenfositopeni (HIV-Negatif AIDS): Olgu Sunumu ve Literatür Derlemesi

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## Abstract

Idiopathic CD4 lymphocytopenia (ICL), also known as non-HIV AIDS, is a rare disease characterized by opportunistic infections, malignancies, and autoimmune diseases. Idiopathic CD4 lymphocytopenia is defined as CD4+ T-lymphocyte level below 300/mm<sup>3</sup> in at least two measurements or less than 20% of total lymphocytes, which cannot be explained by any other condition, including HIV infection. *Nocardia* spp. are opportunistic microorganisms that is a frequent cause of infection in immunocompromised individuals. In this paper, we report a 50-year-old patient with ICL and intracranial brain abscess due to *Nocardia farcinica* and review the literature for related articles published between April 2012 and December 2018. These data suggest that there may be an underlying immunosuppression in adult patients who have infections that are recurrent, refractory, and caused by opportunistic pathogens.

**Keywords:** T-lymphocytopenia, idiopathic CD4-positive, rare diseases, *Nocardia*, nocardiosis

## Öz

Non-HIV AIDS olarak da bilinen idiyopatik CD4 lenfositopeni (ICL) nadir görülen bir hastalık olup fırsatçı enfeksiyonlar, maligniteler ve otoimmün hastalıklarla seyredabilmektedir. İdiyopatik CD4 lenfositopenisi, CD4+ T-lenfositlerin en az iki ölçümde 300/mm<sup>3</sup>'den az ya da lenfositlere oranının %20'den az olması ve bunun HIV enfeksiyonu da dahil başka alternatif durumla açıklanamaması şeklinde tanımlanır. *Nocardia* türleri fırsatçı mikroorganizmalar olup sıklıkla immünokompromize bireylerde enfeksiyonlara yol açarlar. Bu yazıda 50 yaşında, *N. farcinica*'ya bağlı intrakraniyal beyin apsesi ile seyreden bir ICL olgusu sunulmuştur. Ayrıca Nisan 2012-Aralık 2018 tarihleri arasındaki ilgili literatür taraması yapılmıştır. Bu veriler erişkin olgularda tekrarlayan, tedavi edilemeyen ve fırsatçı patojenlerle gelişen enfeksiyonlarda altta yatan bir immünoşüpresyon olabileceğine dikkat çekmek amaçlanmıştır.

**Anahtar Kelimeler:** T-lenfositopeni, idiyopatik CD4-pozitif, nadir hastalıklar, *Nocardia*, nokardiyoz

## Introduction

Idiopathic CD4 lymphocytopenia (ICL) is a rare condition<sup>[1]</sup> that was first described in 1992 by the US Centers for Disease Control and Prevention. ICL is defined as CD4+ T-lymphocyte count below

300/mm<sup>3</sup> or comprising less than 20% of the total lymphocytes in at least two measurements. In addition, it is characteristically unassociated with human T-lymphotropic virus 1 (HTLV-1), HTLV-2, or any primary/secondary immunodeficiency condition, including HIV infection<sup>[2,3]</sup>. Idiopathic CD4 lymphocytopenia has

**Cite this article as:** Aksoy F, Aydın M, Yılmaz G, Güvercin AR, Eyüboğlu İ, Sarı A, Bayramoğlu G, Köksal İ. Idiopathic CD4 Lymphocytopenia (HIV-negative AIDS): Case Report and Literature Review. *Mediterr J Infect Microb Antimicrob*.2019;8:24.



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Received/Geliş Tarihi: 19.12.2018 Accepted/Kabul Tarihi: 16.07.2019

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Mediterranean Journal of Infection, Microbes and Antimicrobials published by Galenos Yayınevi.

**Presented in:** This case is presented as poster announcement in the 6<sup>th</sup> Turkey EKMUD Scientific Platform.

Published: 29 July 2019

also occasionally been referred to in the literature as non-HIV AIDS (NHA)<sup>[4,5]</sup>. Patients with ICL are frequently symptomatic and present with opportunistic infections, malignancies, and autoimmune diseases<sup>[6]</sup>. ICL is usually diagnosed in middle age<sup>[7]</sup>. In patients with opportunistic infections detected in adulthood, the immune system should be evaluated for ICL<sup>[1]</sup>.

*Nocardia* species are opportunistic microorganisms that often cause infection in immunocompromised individuals<sup>[8]</sup>. As the signs and symptoms of infection are mostly nonspecific, there may be delays in diagnosis and treatment. In this study, we present a patient who was diagnosed with NHA and developed an intracranial brain abscess due to *Nocardia farcinica*. Our aim is to highlight the fact that adult patients with recurrent or refractory infections in which opportunistic pathogens are identified, may have an underlying immunosuppressive disease, and that it may not be possible to eliminate these infections unless the underlying disease is identified and treated.

## Case Report

A 50-year-old man had previously presented to another center with a 10-day history of headache and loss of strength in his right leg and right arm. His previous history in that hospital is as follows; brain magnetic resonance imaging (MRI) revealed a mass in the left frontoparietal lobe that was interpreted as metastasis. Thoracic computed tomography (CT), abdominal MRI, and contrast-enhanced cervical, thoracic, and lumbar MRI were performed to investigate whether it was a focal or metastatic mass. Thoracic CT revealed a suspicious lesion in the left lung consistent with malignancy. Pathological examination of a biopsy specimen obtained from the lung lesion was reported as chronic inflammatory fibrotic tissue. One week later, the patient underwent surgery (left parietal craniotomy, tumor excision, and duraplasty) for the intracranial mass. The pathology report indicated brain tissue containing neutrophils, necrosis, and clusters of cellular debris and was primarily consistent with abscess content. Three days after surgery, the patient's complaints regressed and he was discharged with ceftriaxone and metronidazole therapy. However, he presented again with the same complaints 10 days after discharge. Brain MRI revealed a 31-mm diameter area in the left parietal region that could not be defined as mass or abscess, and diffusion MRI showed multiple focal increases in signal intensity in both cerebral hemispheres. The patient was reoperated on the next day (craniotomy, abscess excision, duraplasty). Vancomycin, meropenem, and liposomal amphotericin B therapy was initiated. No microorganisms were identified in cultures obtained in the first or second operations. The results of acid-fast bacilli (AFB) and polymerase chain reaction (PCR) tests for tuberculosis were negative. Thoracic CT scan acquired two weeks after the second operation revealed a 12-cm malignant solid tumor involving

large portions of the upper and lower lobes of the left lung, as well as a reticulonodular pattern suggestive of lymphangitic spread. Left lung lobectomy was performed and the pathology result was reported as inflammatory granulation tissue including suppurative foci (consistent with abscess). Abscess cultures were negative, as were PCR and cultures for tuberculosis. His cerebrospinal fluid (CSF) tested negative for cryptococcal and echinococcal antigens. Cytomegalovirus (CMV) PCR tests were positive in CSF (341200 copies/ml) and serum (1090 copies/ml). However, CMV was not considered as the responsible pathogen and no treatment was given. Indirect hemagglutination test for *Echinococcus granulosus* in the blood was negative. No mass or vegetation was observed on transesophageal echocardiography. Bone marrow aspiration biopsy was reported to be normal. Anti-HIV and HIV-RNA were negative. The patient was hospitalized for 2.5 months and received antimicrobial treatment (ceftriaxone, metronidazole, vancomycin, meropenem, and liposomal amphotericin B) for approximately two months according to his statement and epicrisis report from that center. No pathological examination findings persisted during follow-up except for 4/5 loss of strength in the right upper and lower extremities.

The patient presented to our clinic by his own initiative to continue treatment in our center and was hospitalized for further testing and treatment. His medical history included type 2 diabetes mellitus, tuberculosis 20 years earlier, frequent lung infections, and skin lesions on his scalp that healed and reappeared occasionally until a few years ago.

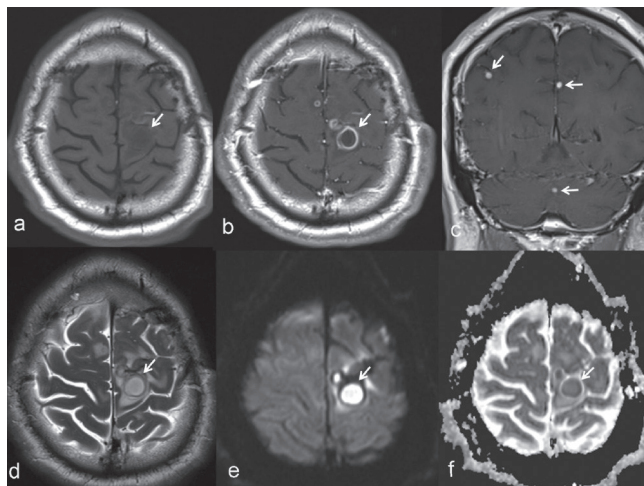
On physical examination, his general condition was good and vital signs were stable. There was 4/5 loss of strength in his right arm and leg. His laboratory tests were as follows: white blood cell count 8290/mm<sup>3</sup>, platelet count 232000/mm<sup>3</sup>, hemoglobin 10 g/dl, hematocrit 28.7%, erythrocyte sedimentation rate 2 mm/h, C-reactive protein 0.5 mg/dl, and procalcitonin 0.17 µg/L. Brain MRI was performed due to his persistent complaints (Figure 1).

He was treated with meropenem and linezolid for 26 days. Because the infectious focus and agent could not be identified during the course of inpatient treatment. However, several tests were planned to investigate underlying predisposing factors. Investigations for immunodeficiency were also performed. These tests revealed that the patient's CD4+ T-lymphocyte count was 263/mm<sup>3</sup> (anti-HIV and HIV-RNA negative). Of the immunoglobulins (Ig), IgG was 371 mg/dl (N: 700-1600) and IgA, IgM, and IgE were normal. Kappa light chain value was 92.9 mg/dl (170-370) and lambda light chain value was 57.5 mg/dl (90-210). Since the patient exhibited no pulmonary findings at admission to our center, no respiratory tract samples (sputum, bronchoalveolar lavage, deep tracheal aspirate) were obtained. Tuberculin skin test and interferon gamma release assay test were not performed. Furthermore, no microbiological testing was done due to the lack of gastrointestinal symptoms such

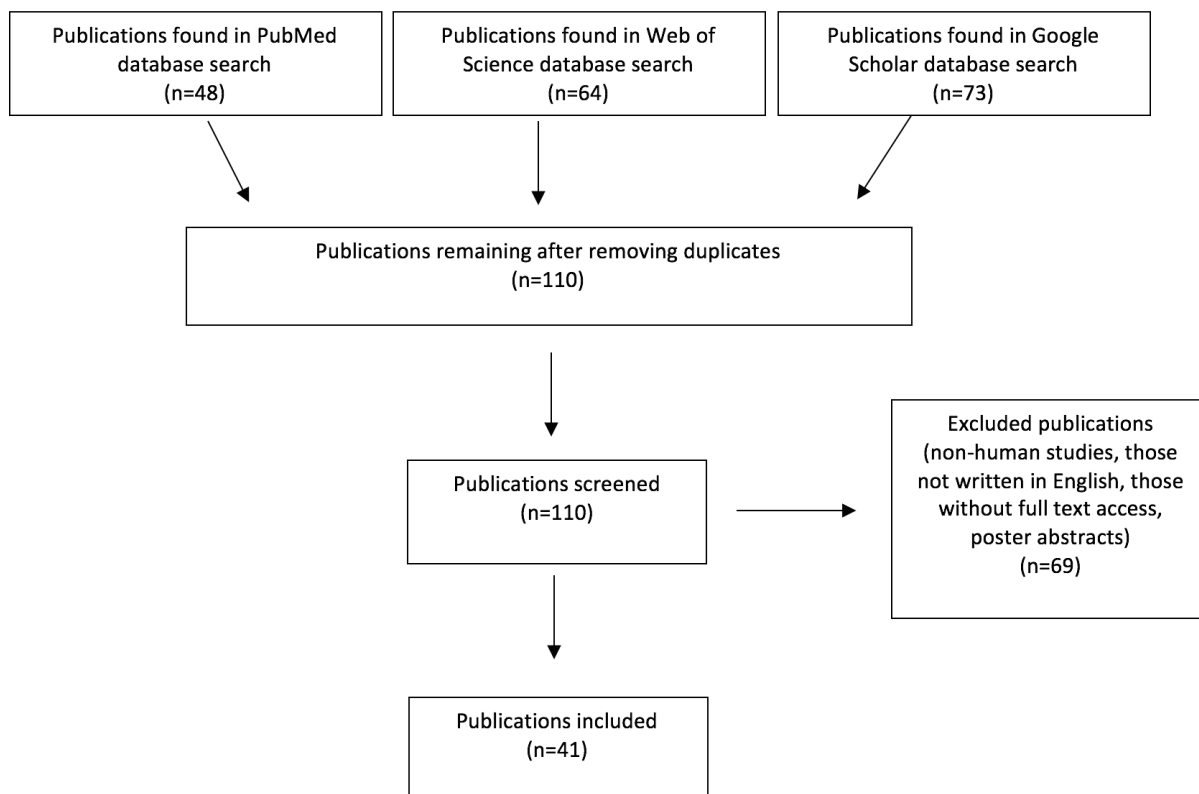
as diarrhea. Suspecting humoral immunodeficiency and ICL, the patient was started on intravenous immunoglobulin therapy once a month. Magnetic resonance imaging was performed again on day 26 of treatment (Figure 2). Since etiological investigations yielded no causative agent, we planned to discontinue antibiotic therapy and repeat the invasive diagnostic tests. After 26 days of inpatient treatment, his antimicrobial therapy was discontinued and he was followed on an outpatient basis. At his 1-week follow-up visit, the patient did not consent to the interventional methods. Thus, further testing could not be done.

He provided consent approximately two weeks after discharge and underwent lumbar puncture. There was no growth in his CSF culture. Acid-fast bacilli and PCR tests for tuberculosis and *Toxoplasma* PCR were negative. Yeast was not detected in India ink screening for cryptococci. CMV PCR was negative in blood and CSF. Diagnostic biopsy of the intracranial lesion was planned, but the patient did not consent to the procedure. The patient was uncooperative regarding testing and treatment, and the inability to obtain samples delayed targeted treatment. There was uncertainty in terms of consecutive treatment (antituberculosis, antifungal, antianaerobic, antistaphylococcal) due to the lack of guiding evidence. Three weeks after discharge, the patient was admitted to the emergency department with fever, weakness in the right arm and leg, and poor general condition. Brain MRI

demonstrated reduction of the bilateral abscess formations in the cerebral and cerebellar parenchyma; however, unlike the



**Figure 1.** Brain magnetic resonance imaging (MRI) at time of admission. The lesion in the precentral gyrus of the left frontal lobe is hypointense on non-contrast T1-weighted axial MRI (a). The lesion shows annular enhancement (arrow) on contrast-enhanced T1-weighted axial MRI (b). Contrast-enhanced coronal T1-weighted image reveals multiple smaller enhancing lesions in the cerebral parenchyma (c). The hypointense ring around the frontal precentral gyrus lesion on T2-weighted MRI examination (d) and its marked diffusion restriction on diffusion MRI (e, f) are consistent with abscess



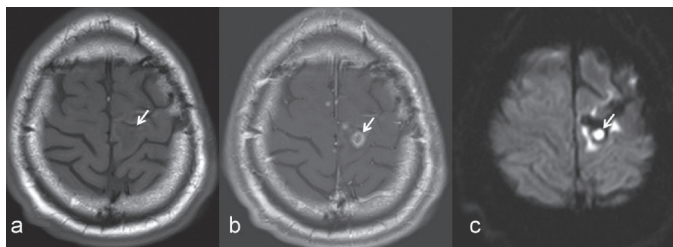
**Algorithm 1.** Flow chart showing the number of publications screened, evaluated for suitability, and included in the study

previous MRI, new abscess formations up to 1.5 cm in diameter showing diffuse right choroid plexus involvement and intense central diffusion restriction were observed (Figure 3). Upon finding that CD4+ T-lymphocyte count was 162/mm<sup>3</sup>, the patient was hospitalized and started on empirical trimethoprim, sulfamethoxazole, meropenem, and antituberculosis therapy for his abscess. On day five of treatment, his general condition deteriorated and he was transferred to the intensive care unit where he was intubated. Two days later, he underwent craniotomy and abscess drainage. *N. farcinica* was isolated in abscess cultures. The pathogen was identified at the species level using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (BrukerDaltonics, Bremen, Germany). Antibiotic susceptibility testing for *N. farcinica* was not performed. Antituberculosis therapy was discontinued and linezolid was added to his treatment. The patient was monitored with mechanical ventilation and died on day 21 of antimicrobial treatment.

### Review of the literature

In March 10, 2019 we searched the literature from April 2012 to December 2018 for articles about ICL and its associated infections. In 2013, Ahmad et al.<sup>[7]</sup> reviewed all cases that occurred until April 2012, so all patients over the age of 18 reported after this date were included in our study. The keywords "idiopathic CD4 lymphocytopenia", "idiopathic CD4+ T-lymphocytopenia", and "non-HIV AIDS" were used to search PubMed, Google Scholar, and Web of Science. The studies evaluated in the literature review are shown in Table 1 and Algorithm 1.

Of the 43 patients evaluated, 34 were male and 9 were female. Their mean age was 47.1±14.3 years and their mean CD4 count was 133.2±86.6/mm<sup>3</sup>. Disseminated infection was observed in 16.3% (n=7) of the cases, while single organ involvement was present in 83.7% (n=36). The most commonly infected organ was the brain (46.5%, n=20), followed by the lungs (18.6%, n=8). The microorganisms most commonly isolated from these infections were *Cryptococcus* species (32.6%, n=14), while



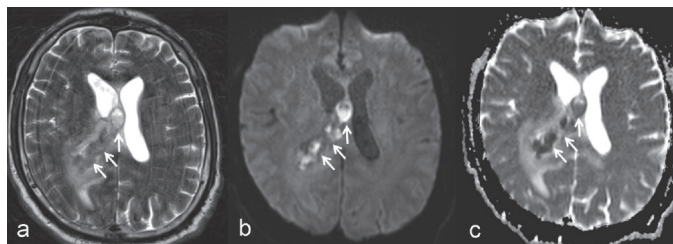
**Figure 2.** Brain magnetic resonance imaging (MRI) after antimicrobial therapy. After antimicrobial therapy, the lesion showing hypointensity on T1-weighted MRI (a) and annular enhancement on contrast-enhanced MRI (b) is reduced in size. Diffusion MRI (c) shows persistent diffusion restriction consistent with an abscess

*Nocardia* species was isolated in 4.7% (n=2). Mortality occurred in 18.6% (n=8) of the cases, with brain involvement in 50% (n=4) of those patients (Table 1).

### Discussion

Idiopathic CD4 lymphocytopenia is characterized by low CD4 count and opportunistic infections<sup>[2,17]</sup>. Idiopathic CD4 lymphocytopenia has also been called NHA and HIV-negative AIDS in the medical literature<sup>[4,5]</sup>. In the presented case, CD4+ T-lymphocytopenia was detected at two different times (263/mm<sup>3</sup> and 162/mm<sup>3</sup>) and HIV antibody and HIV-RNA tests were negative. Before presenting to our hospital, hemograms performed at the other center had also revealed lymphopenia. The patient was diagnosed with ICL based on these findings. Idiopathic CD4 lymphocytopenia is very rare and is usually seen in adulthood<sup>[7]</sup>. Our patient was 50-year-old.

Opportunistic infections are frequent in patients with ICL. In a retrospective study of 24 ICL patients, 71% were found to have opportunistic infections<sup>[50]</sup>. In a review of 258 ICL cases between 1989 and 2012, 87.6% of patients had opportunistic infections and they were most commonly caused by *Cryptococcus* species (26.6%). The second most common infectious agents were *Mycobacterium* species (17%) while the third most common were *Candida* species (16.2%). *Nocardia* species were only detected in two patients<sup>[7]</sup>. Our patient had presented with complaints of headache and loss of strength in his right leg and arm. Abscess culture obtained from the patient during craniotomy and abscess drainage surgery performed due to brain abscess yielded *N. farcinica*, an opportunistic pathogen. *Nocardia* infections are rare and are frequently seen in patients receiving immunosuppressive therapy, organ transplant recipients, or HIV-infected patients<sup>[51-53]</sup>. Nocardiosis is uncommon in immunocompetent individuals, accounting for only 15% of cases<sup>[54]</sup>. People with cellular immunodeficiency are at high risk for opportunistic infections<sup>[55]</sup>. Similarly, ICL was identified as the cause of cellular immunodeficiency in our patient and he also developed intracranial nocardiosis as an opportunistic infection. One of the two cases of nocardiosis found in our



**Figure 3.** Final magnetic resonance imaging (MRI) images. Axial T2-weighted MRI (a) shows lesions in the right choroid plexus with lobulated contour, multicystic features, and hypointense membrane (arrows). On diffusion MRI (b, c), the marked diffusion restriction of the multicystic lesion is consistent with an abscess



**Table 1. Literature review of patients with idiopathic CD4 lymphocytopenia**

Year	Authors (Reference)	Sex	Age (years)	Infectious agent	Affected area	CD4 number (/mm <sup>3</sup> )	Outcome
2012	Ollé-Goig et al. <sup>[9]</sup>	F	30	<i>M. tuberculosis</i>	Lung	28	Death
2012	Colomba et al. <sup>[10]</sup>	M	38	<i>M. abscessus</i>	Disseminated	138	Survival
2012	Rai et al. <sup>[11]</sup>	M	50	<i>C. neoformans</i>	Brain	174	Survival
2013	Yashiro et al. <sup>[12]</sup>	F	49	Cytomegalovirus	Eye	72	Survival
2013	Pavic et al. <sup>[13]</sup>	M	28	<i>C. neoformans</i>	Brain	236	Survival
2013	Delgado-Alvarado et al. <sup>[14]</sup>	M	72	JC virus	Brain	242	Survival
2014	Chumpitazi et al. <sup>[15]</sup>	M	52	<i>Pneumocystis jirovecii</i>	Lung	70	Death
2014	Denu et al. <sup>[16]</sup>	M	57	<i>Rhizopus</i> species	Lung	60	Survival
2014	Ete et al. <sup>[17]</sup>	M	38	<i>Histoplasma</i> spp.	Adrenal gland	216	Survival
2014	Legarth et al. <sup>[18]</sup>	M	59	<i>C. neoformans</i>	Bone (rib)	140	Survival
2014	McBath et al. <sup>[19]</sup>	F	26	West Nile virus	Brain	73	Survival
2014	Nair et al. <sup>[20]</sup>	F	29	Cryptococcal infection	Lung	129	Survival
2014	Sharma et al. <sup>[21]</sup>	M	50	Cryptococcal infection	Skin	165	Survival
2014	Zamani et al. <sup>[22]</sup>	M	26	<i>M. tuberculosis</i>	Disseminated	206	Survival
2014	Monterrubio Villar et al. <sup>[23]</sup>	M	61	CMV	Colon	185	Survival
2015	Adjajian et al. <sup>[24]</sup>	F	70	<i>Nocardia farcinica</i>	Brain	343	Survival
2015	Terrell et al. <sup>[25]</sup>	M	49	<i>C. neoformans</i>	Brain	95	Survival
2015	Sikri et al. <sup>[26]</sup>	M	45	<i>M. tuberculosis</i>	Disseminated	32	Survival
2015	Xia et al. <sup>[27]</sup>	M	38	<i>Penicillium marneffeii</i>	Skin	20	Survival
2015	Ish et al. <sup>[28]</sup>	K	30	Cryptococcal infection	Brain	235	Survival
2016	Aotsuka et al. <sup>[29]</sup>	M	66	JC virus	Brain	84	Death
2016	Ramalingam et al. <sup>[30]</sup>	M	42	<i>M. tuberculosis</i>	Disseminated	250	Survival
2016	Nagar et al. <sup>[31]</sup>	M	32	<i>Pneumocystis jirovecii</i>	Lung	110	Survival
2016	Lim et al. <sup>[32]</sup>	M	66	<i>M. avium intracellulare</i>	Brain	81	Survival
2016	Gupta et al. <sup>[33]</sup>	M	49	VZV	Eye	25	Survival
		M	43	VZV	Eye	133	Survival
2016	Gupta et al. <sup>[34]</sup>	M	33	JC virus	Brain	181	Survival
2017	Malone et al. <sup>[35]</sup>	M	39	<i>C. neoformans</i>	Brain	54	Survival
2017	Panackal et al. <sup>[36]</sup>	M	53	Cryptococcal infection	Brain	14	Survival
2017	Sone et al. <sup>[37]</sup>	M	67	<i>Pneumocystis jirovecii</i>	Lung	257	Survival
2017	Yagnik et al. <sup>[38]</sup>	M	25	<i>Sporothrix schenckii</i>	Disseminated		Death
2017	Perez-Lopez et al. <sup>[39]</sup>	M	64	<i>M. avium intracellulare</i>	Disseminated	7	Survival
2018	Jayaschandran et al. <sup>[40]</sup>	M	46	<i>Nocardia abscessus</i>	Lung	70	Survival
2018	Kano et al. <sup>[41]</sup>	M	70	JC virus	Brain	245	Death
2018	Eshwara et al. <sup>[42]</sup>	M	26	<i>Cryptococcus gattii</i>	Brain	66	Death
2018	Jundt et al. <sup>[43]</sup>	M	60	<i>Pneumocystis jirovecii</i>	Lung	40	Survival
2018	Gupta et al. <sup>[44]</sup>	F	60	<i>Histoplasma</i> spp.	Disseminated	204	Death
2018	Harel et al. <sup>[45]</sup>	F	63	JC virus	Brain	140	Survival
2018	Aghoram and Narayan <sup>[46]</sup>	M	36	JC virus	Brain	110	Survival
2018	Ayub et al. <sup>[47]</sup>	M	45	Cryptococcal infection	Brain	208	Death
2018	Shribman et al. <sup>[48]</sup>	F	33	<i>C. neoformans</i>	Brain	10	Survival
		M	48	<i>C. neoformans</i>	Brain	212	Survival
2018	Nand et al. <sup>[49]</sup>	M	62	Cryptococcal infection	Brain	233	Survival

CMV: Cytomegalovirus, VZV: Varicella-zoster virus

literature review also had brain involvement, like our patient (Table 1). Although physical examination at admission revealed no dermal involvement in our patient, ICL patients presenting with dermal symptoms and findings have been reported<sup>[7,56,57]</sup>. The skin lesions on the scalp described by our patient in his medical history might have been associated with ICL.

There is no standard treatment for ICL. The associated opportunistic infections are treated. Treatments that increase CD4+ T-lymphocyte counts such as interleukin 2 and hematopoietic stem cell transplantation may be used, but the data regarding these approaches are anecdotal and there have been no controlled studies<sup>[58,59]</sup>. Other cytokines like interferon-gamma and interleukin-7 have also been used for treatment<sup>[58,60]</sup>. Since there is no specific and valid treatment was not identified in our case, we could not address the ICL. Hence, we provided symptomatic supportive therapy and treated the opportunistic infection.

Central nervous system involvement is reported in approximately half of disseminated nocardiosis cases in the literature<sup>[61]</sup>, while our patient developed lesions in both the lung and brain (detected in the other center and during follow-up in our hospital). Although *N. farcinica* was isolated from the brain lesion, the lung lesion sample was only sent for histopathological examination and was not cultured; therefore, no microorganism could be identified. However, the lung lesions might also have been nocardiosis. Tumors can be clinically and/or radiologically misinterpreted as abscesses. Therefore, differential diagnosis should be made carefully and microbiological evaluation of tissue samples is imperative<sup>[62]</sup>. Before admission to our center, our patient was followed at another hospital for about 2.5 months and the pathogen responsible for his brain abscess could not be isolated there. When samples are obtained from patients for microbial culture, the microbiology laboratory should be informed about suspected diagnoses. This makes it more likely that the samples will be cultivated in special media under appropriate conditions, thus increasing the chance of isolating the agent. We do not know the culture conditions used at the other hospital. In our hospital, the agent was isolated in both aerobic culture and *Nocardia* culture. Antibiotic susceptibility tests could not be performed. In cases such as this, we believe that isolation of the agent is imperative to enable a more precise approach with targeted treatment.

Combination therapy is recommended for *Nocardia* infections<sup>[55]</sup>. Sulfonamides are the first choice, and alternative therapies include carbapenems, third-generation cephalosporins, and amikacin. The *in vitro* and *in vivo* efficacy of linezolid has also been reported<sup>[63]</sup>. Tigecycline was also shown to be effective *in vitro*<sup>[55]</sup>. Moxifloxacin has been successfully used alone or in combination with other agents in the treatment of brain abscesses caused by *N. farcinica*, which is resistant to various antimicrobial agents. Treatment duration in nocardiosis varies based on

system involvement; the average duration is 6-12 months and treatment is prolonged in patients with central nervous system involvement and those with immunosuppression<sup>[8,64,65]</sup>. In our case, we administered combination antimicrobial therapy with trimethoprim, sulfamethoxazole, meropenem, and linezolid. Because a causative agent could not be isolated as the etiology, we decided to follow the patient without antibiotics for a period of time before performing diagnostic procedures (he had used long-term antibiotics at the other center). He was followed on an outpatient basis but refused interventional procedures other than lumbar puncture. When the patient presented to the hospital again, his clinical presentation had worsened. We attribute this to the inadequate duration of antimicrobial therapy and the lack of treatment for his underlying ICL. Another reason for his lack of response to treatment may be the advanced infection with *N. farcinica*, which is a resistant microorganism.

Immunosuppression may occur in adults for reasons other than chemotherapeutics, immunosuppressants used for rheumatologic diseases, and hematological or solid organ malignancies. The possibility of an underlying immunosuppressive condition should be considered in adult patients with recurrent or undiagnosed infections, and these patients should be evaluated for immunodeficiency. In patients with infections due to opportunistic pathogens, we believe that diagnostic tests should be performed with clinical suspicion of ICL. Furthermore, considering that there are only a few case reports from Turkey, our study makes a significant contribution to the literature.

#### Ethics

**Informed Consent:** The study was a retrospective literature search study and informed consent was not received.

**Peer-review:** Externally and internally peer-reviewed.

#### Authorship Contributions

Surgical and Medical Practices: A.R.G., G.Y., G.B., Concept: F.A., Design: İ.E., A.S., Data Collection or Processing: M.A., Analysis or Interpretation: İ.K., Literature Search: M.A., Writing: F.A., M.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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