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CASE REPORT

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Lymphocyte subsets and the increased risk for opportunistic infections in severe restrictive anorexia nervosa

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Abstract

Restrictive anorexia nervosa (AN-R) is characterized not only by psychiatric manifestations but also by significant medical complications. Patients commonly exhibit immune alterations, potentially increasing their susceptibility to infections. While direct evidence linking AN-R to heightened rates of opportunistic infections remains inconclusive, clinical observations suggest a higher incidence of complications and delayed febrile response in patients with infections. Concurrently, malnutrition, a frequent cause of secondary immunodeficiencies, exacerbates this susceptibility by compromising immune function. This paper investigates the immunological profiles of two patients with long-term AN-R who developed severe infections: one with disseminated *Mycobacterium kansasii* and the other with a co-infection of pulmonary *Aspergillus fumigatus* and *Mycobacterium celatum*. These cases, alongside data collected from previously published case reports summarized in this study, highlight the impact of altered immune function associated with mentioned population. The paper aims to explain the underlying mechanisms of immune dysfunction. Proactive monitoring of immune status and incorporating such assays into clinical practice may benefit early detection, effective management, and ultimately, improved outcomes.

Keywords Anorexia nervosa (AN), Malnutrition, Nontuberculous mycobacterial lung infections, *Mycobacterium kansasii*, *Mycobacterium celatum*, *Aspergillus fumigatus*, Secondary immunodeficiency, Case report

Introduction

Patients with restrictive anorexia nervosa (AN-R) have significantly elevated mortality rates and are known to have many medical complications [1, 2]. The most common findings include metabolic and serum chemistry abnormalities, severe endocrine dysregulation due to the body's adjustment to a low energy state, such as nonthyroidal illness syndrome, functional hypogonadotropic hypogonadism with subsequent amenorrhea, and decreased bone mineral density, presenting as osteopenia or osteoporosis [3]. Various cardiac abnormalities have been documented [4]. Gastrointestinal issues include weakened pharyngeal muscles, gastroparesis, and superior mesenteric artery syndrome. Neurological complications encompass brain matter atrophy, neurocognitive

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deficits, and autonomic nervous system dysregulation (e.g. temperature dysregulation).

The immune system is a complex network of cells, tissues, and organs that work together to defend the body against infections and diseases. The innate immune system provides immediate, nonspecific defense mechanisms against pathogens, including physical barriers like the skin, as well as cells like neutrophils and macrophages that engulf and destroy invading microbes. On the other hand, the adaptive immune system, which includes T and B lymphocytes, provides a more targeted response by recognizing specific pathogens and generating antibodies or cell-mediated responses to eliminate such pathogens. In the context of the infections in individuals with anorexia nervosa that we describe in this paper, alterations in both the innate and adaptive immune system may be involved.

Hematological changes are common in patients with AN, with leukopenia being the most frequent, followed by anemia, typically macrocytic rather than microcytic, and thrombocytopenia [5–7]. Despite the observed leukopenia, patients with AN-R are not commonly believed to experience an increased rate of infection [8]. However, patients with AN-R who have bacterial infections exhibit a diminished fever response, with infection frequency escalating with age. In comparison to controls, patients with AN and infectious complications are more susceptible to prolonged hospital stays [9]. The immune system in this group of patients is largely understudied.

In the two following clinical cases, we describe in detail the immunological changes of two patients with longstanding AN-R with severe opportunistic infections. The first concerns a pulmonary *M. kansasii* infection whilst the other had a *M. celatum* pulmonary infection with concomitant pulmonary *Aspergillosis fumigatus*. The aim of this paper is to highlight the potential mechanisms that underlie altered immune response in patients with AN-R, with respect to T cells and B cells, emphasizing the importance of closely monitoring this group to predict, prevent, and manage immune disturbances and infectious complications. Additionally, it is clinically relevant to recognize patients who might be susceptible to opportunistic infections in order to prevent severe complications.

Clinical cases

M. kansasii *case*

A 51-year-old woman with a decades-long history of AN-R, compulsive personality disorder, Turner syndrome, history of transient ischemic attack, osteopenia, secondary amenorrhea and lymphopenia was evaluated at the Emergency Care Department of Amsterdam UMC and then admitted to the Department of Pulmonology due to recent onset dyspnea, hemoptysis and a 9-month-lasting cough without sputum production. She had not noticed any fever and reported no chest pain. The patient had no known history of pulmonary infections requiring treatment.

Physical examination revealed severe underweight (body mass 35 kg, height 167 cm, and body mass index (BMI) of 12.5 kg/m^2). The patient's vital parameters were recorded as follows: heart rate of 62 beats per minute, blood pressure of 144/86 mmHg, body temperature 35.5 °Celsius, a respiratory rate of 13 breaths per minute and an oxygen saturation of 95% with 5 L of supplemental oxygen. Clinical examination of the chest and abdomen was unremarkable, as well as auscultation of the heart and lungs. Laboratory investigation revealed anemia (hemoglobin: 6.9 mmol/L), mild leukopenia (4.1×10^9/L), normal platelet count (281×10^9/L), with electrolytes within normal range (sodium 133 mmol/L, potassium 3.6 mmol/L). Her liver enzymes were diffusely elevated without increased bilirubin, CRP was normal and ANCA titers were low. A high resolution CT scan of the chest (Fig. 1) revealed a thick walled, cavitating consolidation at the right upper lobe with surrounding bronchiolitis.

Initial results of cultures of sputum and bronchoalveolar lavage (BAL) fluid showed no pathogens. Because of persistent hemoptysis and uncertainty about the diagnosis, patient underwent uniportal video-assisted thoracic surgery for lobectomy of the right upper lobe, which was complicated by an empyema. Subsequently, cultures of the pleural fluid and the resected tissue were found positive for *Mycobacterium. kansasii.* Patient was initially treated with empiric antibiotics (amoxicillin-clavulanic acid), which was changed to the combination of rifampicin, ethambutol, and isoniazid for better coverage of the mycobacterial infection. Pyridoxine was started to prevent neuropathy in addition to thiamine that was prescribed during refeeding. Due to difficulties in obtaining appropriate dosages for the patient's low weight, isoniazid monotherapy was initiated one month later in the treatment course.

Additional laboratory investigation revealed severe deficiency in absolute numbers of B cells (0.004×10^9/L, presenting 0.86% of all lymphocytes). Absolute counts of all T cells (CD3 + 0.318×10^9/L; CD4 + T cells 0.187×10^9/L and CD8 + T cells 0.101×10^9/L) were low. However, percentages of T lymphocytes were within normal values including a normal CD4 + /CD8 + ratio of 1,8. Further immunophenotyping was conducted on B cells, and T cells. No hypogammaglobulinemia was present. Further immunological assessment concluded patient had no known immunological disorder that could explain longstanding lymphopenia and opportunistic infection other than malnutrition. The total duration of treatment

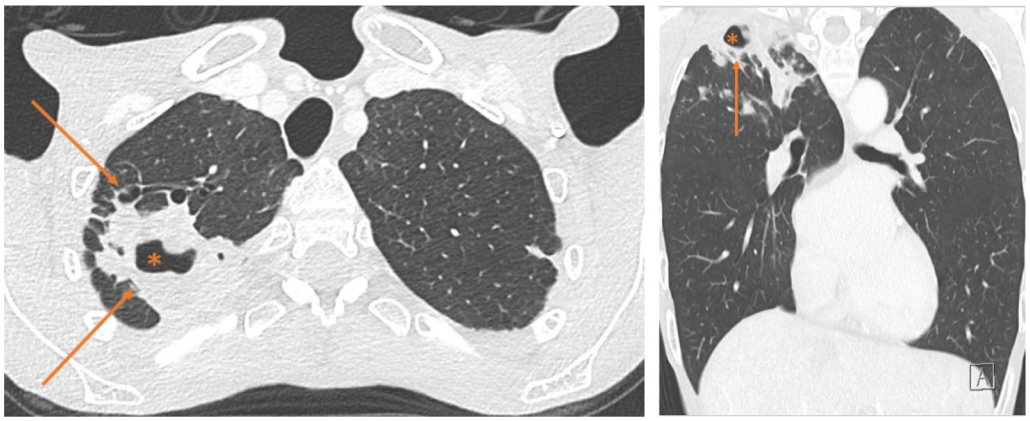

Fig. 1 CT chest of patient 1 at the presentation. Thick walled, cavitating consolidation (orange arrow and orange *) at the right upper lobe with surrounding bronchiolitis

for *M. kansasii* infection was 1 year, and the patient responded to antibiotic treatment with no side effects. Nutritional support was also provided to address her severe malnutrition.

Over the months after admission, the patient showed gradual improvement in nutritional status, evidenced by weight gain and a rise in BMI to 14.0 kg/m^2 in 11 months. Laboratory analysis revealed resolution of leukopenia at the time of weight gain. Absolute numbers of T cells normalized, including normalization of CD8+T cells and CD4+T cells, and absolute numbers of B lymphocytes normalized (100-fold). NK cell numbers increased. 26 months after admission, the patient lost weight again, her BMI fell to 12.4 kg/m^2 and the subgroups of lymphocytes declined in absolute numbers again below reference values (Fig. 2).

M. celatum and A. fumigatus case

A 44-year-old female patient who also had a decades-long history of AN-R, autism spectrum disorder, anxiety/compulsive disorder, spastic colon/irritable bowel syndrome, secondary amenorrhea and osteoporosis presented with cough, hemoptysis and night sweats and was evaluated at another center. Four months prior, she was

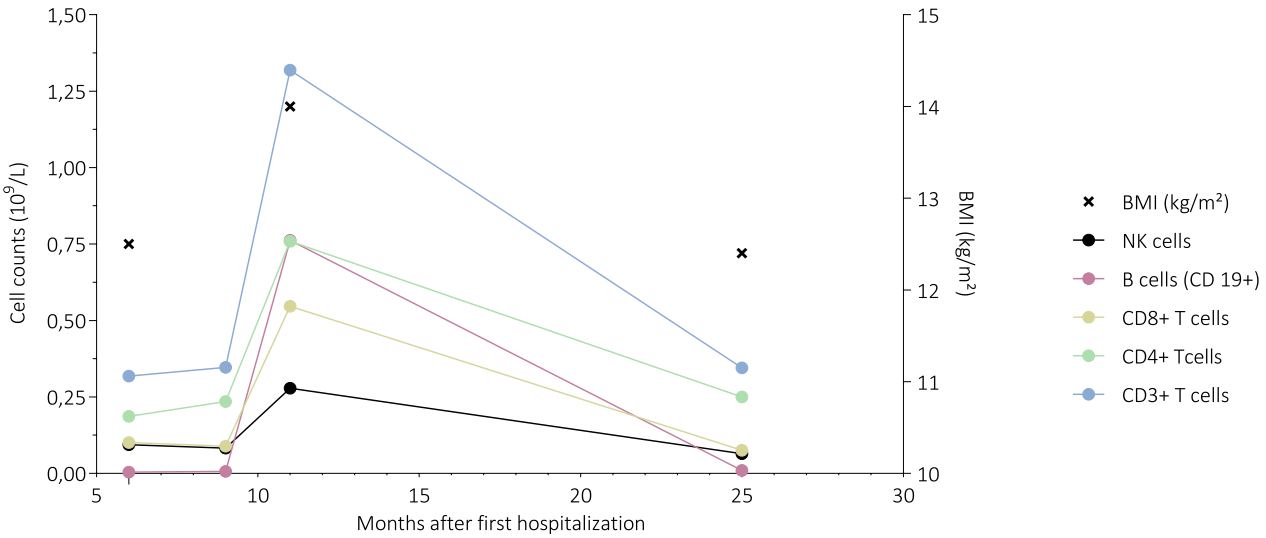

Fig. 2 Overview of the dynamics of patient 1 BMI and absolute number of subsets of lymphocytes; B cells, all T cells (CD3+), CD8+T cells, CD4+T cells, natural killer (NK) cells over time since start of disease. Lymphocyte subsets are presented in absolute counts measured in whole blood. X-axis shows number of months after admission, left Y-axis lymphocyte counts and the right Y-axis BMI (body mass index) in kg/m^2. The reference values are as follows: T cells (CD3+) range from 0.7 to 2.1×10^9 cells/L, CD4+T cells range from 0.3 to 1.4×10^9 cells/L, CD8+T cells range from 0.2 to 0.9×10^9 cells/L, B cells range from 0.1 to 0.5×10^9 cells/L, and NK cells range from 0.09 to 0.6×10^9 cells/L

hospitalized due to severe malnutrition requiring short-term refeeding.

Physical examination revealed severe underweight. Her body weight was 28.5 kg, height 160 cm, and BMI 11.1 kg/m^2, with lower limb edema. The patient's vital parameters were: heart rate of 60 beats per minute, blood pressure of 79/63 mmHg, and body temperature of 37 °C.

Laboratory results indicated anemia (hemoglobin 7.0 mmol/L), normal leukocyte count ($7{,}500 \times 10^9$/L), and normal platelet count (291×10^9/L). Further laboratory investigation revealed lymphopenia with a total lymphocyte count ranging from 0.48—0.60 cells/10^9/L. Due to a suspected *Mycobacterium tuberculosis* infection and abnormalities on her chest CT (Fig. 3), BAL was performed and confirmed the presence of both *M. celatum* and *A. fumigatus*.

A multidisciplinary team decided to prioritize treatment for the *A. fumigatus* infection above tuberculostatic treatment, as the mycobacterium was deemed capable of self-clearance. Voriconazole was initiated. Despite receiving treatment, her condition showed no improvement over consecutive months. During this period further laboratory tests examined lymphocytes characteristics and revealed a low total T cell count, (ranging from 0.32 to 0.34×10^9 cells/L), low CD8 + T cells (0.065 to 0.087×10^9 cells/L) and low CD4 + T cells (0.26 to 0.28×10^9 cells/L). Further immunophenotyping was conducted on CD4 + T cells, and CD8 + T cells. The patient's B cell count was very low ($0.010–0.015 \times 10^9$ cells/L), and the CD4 + /CD8 + ratio was elevated to 4.4 due to very low CD8 + cells rather than elevated CD4 + cells. The neutrophil count was normal ($5.77–6.34 \times 10^9$cells/L).

After seven months, due to persistent symptoms and difficulties in controlling infections in an outpatient setting, the patient was readmitted for one month to initiate treatment for chronic pulmonary aspergillosis (CPA). Voriconazole was switched to micafungin due to a panazole-resistant strain of Aspergillus found in sputum culture. By month 14, significant progression of her lung lesions was observed on the chest CT. Her weight remained low at 33 kg. Treatment for NTM was not possible due to low body weight, and the patient agreed to be admitted on the medical psychiatry unit to improve her nutritional status, initiate NTM treatment, and continue treatment for Aspergillus. Her weight at the time was 32.2 kg, BMI 13.2. One month after intensive refeeding, ethambutol, clofazimine, and azithromycin were started to treat the NTM infection. Amikacin was initiated for two months, and micafungin continued. A screening test for chronic granulomatous disease, in which Aspergillus infections are common, showed a normal oxidative burst of neutrophils and thus normal overall metabolic integrity of phagocytic neutrophils. Further immunological assessment concluded that our patient had no known immunological disorder other than malnutrition that caused immunodeficiency. She was discharged in April 2024; her weight had by that time increased to 40.3 kg, BMI 16.6, and her overall health radically improved. At that time laboratory analysis revealed resolution of leukopenia. Absolute count of lymphocytes, CD3 + T cells and CD4 + T cells rose but remained under reference values. The absolute number of CD8 + T cells and B lymphocytes normalized whereas the NK cell number increased.

Discussion

This report presents two cases of severe opportunistic lung infections with *Mycobacterium species* and *Aspergillus* that occurred in patients with immunodeficiency attributable to malnutrition caused by longstanding AN-R including the dynamics of CD8 + T cells, CD4 + T cells, and B cells that corresponded with the fluctuation in body weight.

Changes in peripheral blood cell count are often seen in AN-R which is true for red and white blood cells, as well as platelets [69]. Mild leukocytopenia is common and alterations in T- and B-cells can be found. Bone marrow

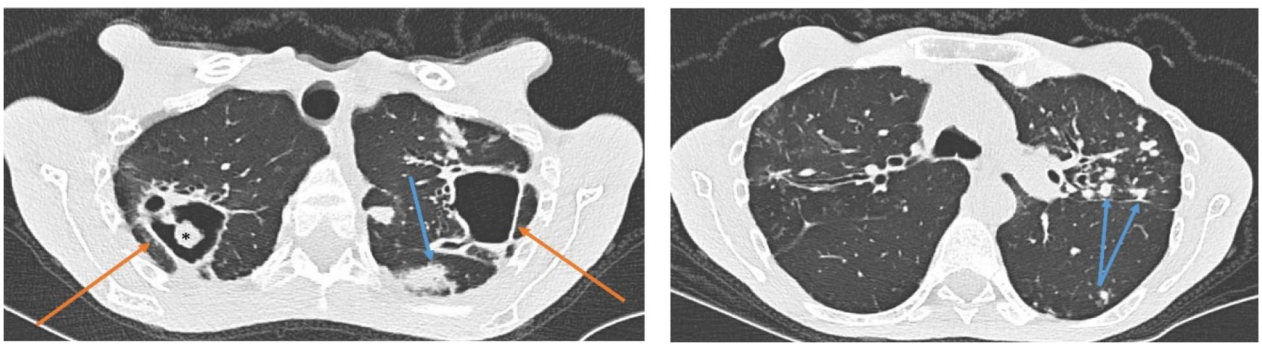

Fig. 3 CT chest of patient 2 in the first months of presentation. Large, bilateral cavitary lesions (orange arrows) with polypoid growth (*) at the right upper lobe. In addition, several dense consolidations / nodules (blue arrows), most present at the left upper lobe and lingula

atrophy and gelatinous transformation (complete atrophy and deposition of amorphous material) are characteristic findings in AN-R and associate with low body fat and may be present half of the patients. These hematological and morphological changes resolve completely and rapidly after refeeding.

Mycobacterium species other than *M. tuberculosis* and *Mycobacterium leprae* constitute nontuberculous mycobacteria (NTM), also termed atypical mycobacteria. The predominant causative agent of NTM infections in humans is *Mycobacterium avium complex* (MAC). The incidence of NTM infections is increasing worldwide in part due to aging [10]. The individuals that are typically at risk to become infected by NTM usually suffer from immune defects or underlying lung diseases such as cystic fibrosis or chronic obstructive pulmonary disease [11]. A retrospective, descriptive study of 182 patients suffering from non-tuberculous mycobacteria (NTM) identified elderly females, particularly those with low BMIs, as a new population at risk for NTM [12]. As expected, a lower BMI appears to independently increase the risk of pulmonary NTM infection [13]. Furthermore, several case reports indicate that malnutrition due to AN may form a risk factor for NTM infections (Table 1).

Similarly, *A. fumigatus*, a common soil-dwelling fungus prevalent in various environments including organic debris, dust, and rotted plants, typically causes no disease in immunocompetent individuals [39]. The clinical presentation of Aspergillus-related infections varies widely, and is largely influenced by the underlying immune status and possible pulmonary disease. This spectrum ranges from acute bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, bronchitis, acute community-acquired, chronic cavitary nodules/aspergilloma to invasive disease in severely immunocompromised individuals [40]. Chronic pulmonary aspergillosis primarily affects individuals with underlying lung conditions like chronic obstructive pulmonary disease, sarcoidosis, or a history of tuberculosis or non-tuberculous mycobacterial disease [41]. Underlying immunosuppression that causes heightened susceptibility to disease caused by Aspergillus is directly proportional to neutrophil dysfunction and reduced number of neutrophils [5]. Of note, our patients did not receive *Pneumocystis jirovecii* pneumonia prophylaxis, although these infections have been reported in AN-R (Table 1).

Both of our patients experienced opportunistic infections that are typically harmless in healthy individuals but become pathogenic when the body's defense system, e.g. number of B and T lymphocyte, weakens [42]. The most commonly observed and clinically significant immune system abnormalities in patients with AN are a reduced total white blood cell (WBC) count and impaired WBC function [8]. Absolute lymphocyte count is shown to be reduced as observed in both of our patients. Cell-mediated immunity is more affected than humoral immunity in AN-R. T-cell absolute counts are notably reduced [43]. Furthermore, it has been shown that the function of cell-mediated immunity, assessed via the delayed hypersensitivity skin test, is diminished. Additionally, there are alterations in T-lymphocyte subsets [44]. While both CD4 + and CD8 + T cell subtypes are decreased in malnourished children [45], patients with AN are found to present with increased CD4/CD8 T cell ratios due to a more significant reduction in CD8 + T cell counts compared to reduction in CD4 + T cell count [46–48]. Our patients showed reduced WBC, reduced total absolute lymphocyte counts, and reduced absolute counts of CD4 + and CD8 + T cells (Fig. 4). An increase in CD4/CD8 T cell ratio was seen in patient 2.

Several studies have found that total B cell count and relative B cell count in individuals with AN (without infection) are equivalent to those in healthy controls [46, 49]. A more recent study even reported increased total B cell counts, though the percentages remained comparable to those in healthy adolescents [50]. However, in both patients presented in this paper, the B cell count was significantly decreased. Similarly in a study of lymphocyte subsets in malnourished and well-nourished children with bacterial infections, B lymphocytes in malnourished children showed significantly lower values in relation to the results seen with well-fed children [45]. Interestingly, patient 1 displayed a 100-fold increase in total B cell count following refeeding and weight gain. Neutropenia is usually present as well [51, 52]. A study of individuals with anorexia nervosa compared to healthy controls found significant deficit in functions of neutrophils chemotaxis and adherence as well as deficit in granulocyte microbiocidal activity [53]. Lower absolute counts of NK cells are observed in patients with eating disorders, including both restrictive and binge-purge types as supported by both our patients [54].

Malnutrition stands as the primary cause of secondary immunodeficiency globally [55], and it has been linked to immune dysfunction in a variety of settings, including starvation and cachexia in both human beings and animals [56]. There are different mechanisms that may contribute to the AN-R related immune dysfunction. Firstly, immune cells such as lymphocytes rely heavily on glucose uptake [57]. When leukocytes are in a non-activated (resting) state, energy is derived from lipid oxidation and complete oxidation of glucose through the TCA cycle where energy is generated through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins. However, during immune activation, leukocytes increase glucose utilization, switching from complete

Table 1 Anorexia and secondary immunodeficiency: cases

Author and year	Age	Gender	BMI kg/m2	Infection type disease	WBC and subtypes	Treatment/ management	Outcome
Pulmonary infections							
Brown [14] 1987	21	Female	13.0	*Mycobacterium xenopi*, pulmonary infection	/	nutritional support azithromycin rifampin ethambutol	Full recovery and recovery of BMI to 17.5
Walsh, Baca [15] 2014	53	Female	14.2	*M. Avium*-intracellulare pulmonary infection	WBC 7200 cells/mm^3 neutrophils 74%, lymphocytes 13%, monocytes 10%, eosinophils 2%, basophils1% CD4+T cell 272/ mm^3, 45% of the total T-cell population	Azithromycin rifampin ethambutol	Full recovery
Alhanna, Purucker [16] 2012	27	Male	11.8	*Mycobacterium chimaera*, necrotizing liquefying pneumonia	WBC 4500 cells/mm^3	clarithromycine rifabutine ethambutol	Progression and surgical removal of the upper left lobe
MacNeil, Hudson [17] 2020	31	Male	18.0	*M. kansasii* , pulmonary infection	/	Isoniazid rifampicin moxifloxacin	Full recovery
Hotta, Minami [18] 2004	21	Female	10.0	*Mycobacterium szulgai*, pulmonary infection	WBC 5200 cells/mm^3 lymphocyte 1700 cells/mm^3 granulocyte 3245 cells/mm^3	isoniazid rifampsin ethanbutol	Death after suffocation on sputum at home 1 month after being discharged
Cosson, Bertrand [19] 2012	20	Female	14.5	*M. kansasii*, pulmonary infection	WBC of 3800 cells/mm^3	rifampicin ethambutol	Full recovery and weigh restoration of BMI to 20.5 kg/m2
Grayeb, Chan [20] 2021	54	Female	15.0	*M. abscessus*, lung disease	/	nutritional rehabilitation clofazimine amikacin imipenem-cilastatin	Weight restoration, partial lung resection
Grayeb, Chan [20] 2021	41	Female	11.1	*M. abscessus* complex recurrence of pulmonary MAC	/	azithromycin ethambutol and rifampin moxifloxacin streptomycin lobectomy	Discharged with nutritional plan
Grayeb, Chan [20] 2021	41	Man	16.0	*M. abscessus* complex, pulmonary infection	mild leukopenia	azithromycin ethambutol rifampin	Full recovery
Tenholder and Pike [21] 1991	28	Female	*41 kg**	*M. xenopi*, pulmonary infection	WBC 5200 cells/mm^3	dietary therapy Isonazide rifampin	Improved roentgenogram, negative cultures
Oshima, Niinuma [22] 2021	46	Female	10.2	*Mycobacteria marinum*, pulmonary infection	WBC 4700 cells/mm^3 lymphocyte 799 cells/mm^3	rifampicin clarithromycin	Radiographic improvement, increase in weight to 11.7 BMI
Shah, Siglin and Patel [23] 2020	40	Female	16.8	*M. szulgai* bilateral pulmonary infection	WBC 15700 cells/mm^3 lymphocyte 330 cells/mm^3	intubation and mechanical ventilatory support moxifloxacin, ethambutol and rifabutin	Developed treatment side effects, admitted to psychiatric hospital for body weight restoration

Table 1 (continued)

Author and year	Age	Gender	BMI kg/m2	Infection type disease	WBC and subtypes	Treatment/ management	Outcome
Mogi, Kosaka [24] 2012	31	Female	12.5	Aspergillus, pulmonary aspergilloma	/	segmentectomy	Uneventful recovery
Takushima, Haraguchi [25] 2004	27	Female	15.0	Aspergillus, pulmonary aspergilloma	/	lobectomy	VATS lobectomy was safely performed, lobes expanded very well
Shimoni, Goldenberg and Niven [26] 2006	29	Female	*20 kg**	*Aspergillus niger* Klebsiella	WBC 7600 cells/mm^3 neutrophils 95%	Ceftriaxone amphotericin B	Intubated and mechanically ventilated, died from cardiovascular collapse hours after intubation
Enriquez-Estrada, Tapia-de la Barrera [27] 2019	23	Female	13.0	*A. fumigatus*	/	nutrition rehabilitation, antibiotics, olanzapine	/
Mogi, Kosaka [24] 2012	31	Female	12.5	*A. fumigatus* , pulmonary aspergilloma	/	segmentectomy	Full recovery
Pejčić, Stanković [28] 2012	44	Female	12.3	*Aspergillus Hyphae*, chronic necrotizing pneumonia	leukocytes normal, neutrophils 3200 cells/mm^3	voriconazole	Gained weight, good general condition, changes on her lungs were stationary
Yoshinouchi, Yamamoto [29] 2023	young	Female	10.1	*Exophiala dermatitidis*, *E. dermatitidis* pneumonia	WBC 9600 cells/μL neutrophils of 8200 cells/μL lymphocytes of 800 cells/μL monocytes of 200 cells/μL	nutritional support voriconazole itraconazole clarithromycin	Discharged on day 133 and continued on oral itraconazole for 3 months
Hanachi, Bohem [30] 2018	51	Female	12.3	*P. jirovecii* pneumonia	leukocytes 2000/ mm^3, lymphocytes 410 / mm^3 CD4 + T cells 138 / mm^3, CD4 + /CD8 + ratio of 1.10	nutritional therapy sulfamethoxazole/ trimethoprim	Discharged to a specialized Eating Disorders Nutritional Unit for enteral nutrition
Attalla El Halabieh, Petrillo [31]2014	71	Female	16.9	*P. jirovecii* , pneumonia	lymphocytes 599/mL CD4 + T cells 94 cells/μL(low) CD4 + /CD8 + ratio 1.13	TMP/SMX levofloxacin vankomycin corticosteroids parenteral nutrition	Thrombocytopenia and DIC developed, and the patient died of respiratory failure
Hotta, Nagashima [32] 2004	21	Female	11.8	*M. tuberculosis*, Pulmonary tuberculosis	WBC 6200/μL Granulocyte 76%, 4768/μL Lymphocytes 11.6%, 719/μL CD4 25%, CD8 41%	Isoniazid rifampicin ethanbutol	After 6 months improvement on CT
Nervous system infections							
Tamura, Kawamoto [33] 2020	17	Female	14.7	*Candida guilliermondii*, chorioretinitis	WBC 2000–3000/μL neutrophils 500–1000/μL (low)	central parenteral nutrition therapy, micafungin, cefazolin, fosfluconazole	Improvement of chorioretinitis, negative blood cultures were confirmed

Table 1 (continued)

Author and year	Age	Gender	BMI kg/m2	Infection type disease	WBC and subtypes	Treatment/ management	Outcome
Ahn, Chang [34] 2007	23	Female	15.6	*M. tuberculosis* disseminated tuberculosis, intracerebral granulomas	WBC 3,220/mm3, neutrophils 75.4% lymphocytes 13.5%, helper T-cell (CD4) 25% cytotoxic T-cell (CD8) 32%, CD4/CD8 ratio of 0.78	isoniazid(INH), 450 mg rifampin (REP), 600 mg ethambutol(EMB), and 2.0 g pyrazinamide (PZA) temporoparietal craniotomy	Tuberculomas persisted, increase in body weight, symptoms were completely resolved
Yoshida, Matsuda [35] 2022	28	Female	10.8	*Candida albicans*, Abscess in brain lung, anterior chest wall and bilateral iliopsoas muscles	WBC 9700/μL	fosfluconazole, fluconazole, amphotericin B, flucytosine, craniotomies for drainage	Severe frontal lobe dysfunction persisted
Other infections							
Komatsu, Hayashi and Higashiyama [36] 2017	13	Female	11.0	Enterobacter cloacae Sepsis, neutropenia	WBC 3470/μL (day 1) and 1780/μL (day 8) absolute neutrophil count (ANC) 2050/μL(day 1), 890/μL (day 7)(low) after refeeding declined to 346/μL	G-CSF ceftriaxone	Transferred to a special hospital for AN on day 60 of hospitalization, ANC had increased to 1000/μL or more and remained stable
Suda, Nagamitsu [37] 2017	12	Female	13.0	Acinetobacter baumanii, DIC	WBC 5000/μL neutrophil count: 652/μL	Nutritional treatment, human serum albumin γ-globulin	4 days after administration of γ-globulin, her platelets rose
Hotta, Nagashima [32] 2004	22	Female	15.5	*M. tuberculosis*, Extrapulmonary tuberculosis	WBC 7000/μL granulocyte 77,8%, 5446/μL lymphocyte 15.5%, 1085/μL	isoniazid rifampicin ethanbutol	After 6 months improvement on CT
Duong and McKillion [38]	41	Female	/	Histoplasma capsulatum disseminated histoplasmosis, spontaneous bacterial peritonitis, Clostridium Difficile colitis	/	nutritional support amphotericin B piperacillin-tazobactam, vancomycin, meropenem, ampicillin	

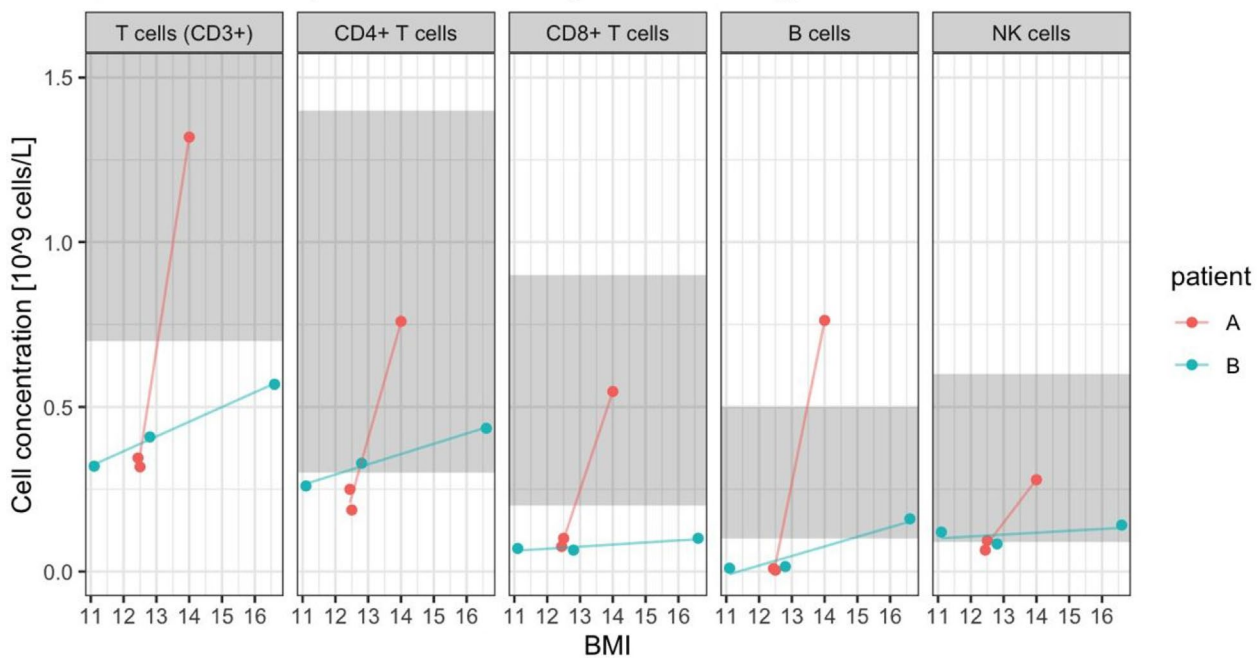

Fig. 4 Absolute cell numbers of lymphocyte subsets in two patients: Patient 1 (red dots) and Patient 2 (blue dots), plotted against BMI. The gray areas represent the reference values for each lymphocyte subtype. A positive association between BMI and cell number is observed across all lymphocyte subtypes in both patients

oxidation of glucose to glycolysis and increased pentose phosphate pathway (PPP) flux, which supports cell proliferation by providing necessary glucose-derived products [58]. This shift from oxidative to glycolytic metabolism is critical to maintain T cell function, as decreased glucose availability inhibits T cell cytokine production and proliferation [59]. Several studies have specifically examined the effect of malnutrition on T cell number and function and found decreased T cell numbers fasted mice and in malnourished humans [45, 60]. This suggests that decreased circulating glucose levels during fasting may directly impact T cell metabolism and, consequently, T cell function. Glucose is also vitally used in other immune cells: through the PPP, glucose produces nicotinamide adenine dinucleotide phosphate (NADPH), required by macrophages and neutrophils to generate radicals that kill bacteria and facilitate phagocytosis [58]. In anorexia nervosa (AN), low glucose levels and depleted energy reserves impair glucose availability. In patient 1, absolute counts of lymphocyte subsets normalized shortly after refeeding, although BMI remained in the range of severe AN, which further establishes the importance of available glucose for immune function.

Secondly, neuroendocrine changes may play a role in T and B cell changes. Leptin is an adipokine secreted in proportion to adipocyte mass. In addition to its well-described role in regulating appetite, energy expenditure, and body weight, leptin is also a pro-inflammatory cytokine. Leptin modulates the immune system by promoting T-lymphocyte differentiation, enhancing phagocyte function, and increasing the production of the cytokines TNF-α and IL-12. Moreover, leptin promotes the Th1 immune response by promoting secretion of IFN-γ [61]. In AN-R, levels of leptin are reduced and therefore all the functions above are limited. Leptin-deficient mice have delayed clearance of *Mycobacterium abscessus* lung infection compared to wild-type mice [62]. Due to its role in stimulating the gonadal axis, reduced leptin secretion is also implicated in decreased estrogen production and the commonly observed amenorrhea in patients with AN-R [63]. Experiments in ovariectomized mice indicate that estrogen enhances the clearance of *M. Avium Complex* [64], the most common agent causing NTM infection in humans. From data collected from human studies, no definitive conclusions can be drawn [65]. One can speculate that lowered leptin and estrogen levels observed in AN patients could potentially correlate with increased susceptibility to infections, especially to NTM infections.

Additionally in AN, the bone marrow undergoes changes known as gelatinous marrow transformation (GMT) known also as starvation marrow. GMT is characterized by marrow hypoplasia and the interstitial infiltration of a gelatinous substance composed of acidic

mucopolysaccharides [66]. GMT is linked to the degree of weight loss in AN, reflecting the patient's nutritional status.

Normally, commensal bacteria in the gut play a crucial role in maintaining immune system health and tolerance through metabolite production, such as butyrate, which supports gastrointestinal epithelial cells. In AN, changes in the microbiota, including decreased production of short chain fatty acids and disruption of the intestinal barrier, can lead to increased activation of the immune system. This dysregulation, coupled with potential decreases in immune tolerance and increased pro-inflammatory cytokine production, may contribute to susceptibility to infections and gastrointestinal disturbances in individuals with AN [67].

Given the heightened risk of infectious complications and reduced febrile response in severe AN patients, early detection methods are imperative [52, 68]. The decrease in lymphocyte subsets (B cells, CD4 + T cells, CD8 + T cells) in patients with AN-R may be one of the indicators of heightened risk for opportunistic infections and complications. Moreover, refeeding and weight gain lead to the normalization or rise of absolute lymphocyte subset numbers.

At this moment, it is difficult to provide pragmatic guidance for what age, fat mass, or hematology lab results should prompt further evaluation of lymphocyte subtypes. However, if these subtypes are analysed and proven to be low, then a high degree of concern for risk of mycobacterial-like infections may be raised. Likewise, the presence of the infections may warrant analysis of lymphocyte subsets which underscores the relevance of periodic clinical assessment. Alternatively, assessment of the lymphocyte count alone may be sufficient. Future studies will need to evaluate if and how lymphocyte subsets can predict the increased risk for opportunistic infections in AN-R.

Author contributions

PV MRS wrote the main manuscript text PV prepared figures EMvL performed lab work on blood cells MRS, CV, JA, ACMvB and GJdB performed clinical tasks on the patients All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Consent for publication

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Competing interests

The authors declare no competing interests.

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