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NOVEL ID CASES

Treatment Dilemmas in Disseminated Nontuberculous Mycobacterial Infections With Interferon-gamma Autoantibodies

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Disseminated *Mycobacterium avium* complex (dMAC) is typically seen in individuals with impaired cell-mediated immunity and is best described in those with HIV. Recently, cases have been described in otherwise healthy individuals with neutralizing antibodies to interferon-gamma (nIFNγ-autoAb), especially in patients of Southeast Asian descent. Treatment is often refractory to mycobacterial therapies, and the use of rituximab and other immunomodulatory agents has been explored. We report 3 cases of dMAC with nIFN-γ-autoAb and review the available literature on treatment strategies to provide a framework for the management of patients with refractory infections in the context of neutralizing antibodies to interferon-gamma.

Keywords. disseminated; interferon-gamma autoantibody; mycobacterium avium complex; nontuberculous mycobacterium.

CASE DESCRIPTIONS

Patient 1

A 44-year-old Filipina woman presented with 5 months of constitutional symptoms, lymphadenopathy, elevated liver enzymes, and pancytopenia. She was found to have disseminated *Mycobacterium avium* complex (dMAC) involving the lungs, liver, lymph nodes, and bone marrow (Figure 1). After initial negative immunodeficiency workup, neutralizing antibodies to interferon-gamma (nIFNγ-autoAb) were strongly positive. She was treated with azithromycin, ethambutol, and rifabutin.

Despite adherence to therapy, her disease progressed with persistent constitutional symptoms, lymphadenopathy, and sputum culture positive for MAC. After 4 months of therapy, she developed hemoptysis secondary to an erosive paratracheal lymph node. Biopsy of the node cultured positive for MAC, which remained susceptible to macrolides. Rituximab (375 mg/m^2 monthly for 2 months) was added to her antimicrobial therapy, followed by prompt improvement in her symptoms and clearance of sputum cultures. After 2 years of therapy, neck/chest computed tomography (CT) showed no residual disease, nIFNγ-autoAb were decreased but not normalized, and she discontinued therapy. Six months later, she remains asymptomatic without evidence of relapse.

Patient 2

A 53-year-old previously healthy Cambodian woman presented with 3 months of constitutional symptoms, nausea, and vomiting with omental caking, nodularity, and retroperitoneal lymphadenopathy on abdominal CT (Figure 2). Biopsy of an intraabdominal lymph node was culture positive for MAC, and immune workup revealed nIFNγ-autoAb. Because of her inability to tolerate oral medications, she was initially treated with parenteral azithromycin, rifampin, amikacin, and moxifloxacin. Amikacin was stopped after 4 weeks due to sensorineural hearing loss.

After 3 months in the hospital without improvement despite antimicrobial therapy, rituximab (375 mg/m^2 weekly for 4 weeks) was initiated, followed by marked clinical improvement. She was discharged 6 weeks later on azithromycin, ethambutol, rifampin, and interval rituximab. She discontinued antimycobacterial therapy at 22 months and remains well 8 months later with persistent but improved omental stranding and mesenteric lymphadenopathy on imaging.

Patient 3

A 53-year-old Filipino man with a history of nontyphoidal *Salmonella* bacteremia presented with 12 months of cough, lymphadenopathy, back pain, and weight loss. He was found to have dMAC involving the lung (Figure 3), lymph nodes, and spine. Sputum and blood cultures were positive for MAC and immune evaluation strongly positive for nIFNγ-autoAb. He was started on azithromycin, rifabutin, ethambutol, and moxifloxacin with initial clinical improvement and clearance of blood cultures. Moxifloxacin was eventually stopped due to tendonitis.

Six months later, he developed new bulky lymphadenopathy in the left neck and axilla. Lymph node biopsy was culture positive for *Mycobacterium abscessus* subsp. *massiliense* and was susceptible to amikacin, clarithromycin, and clofazimine, with intermediate susceptibility to linezolid and cefoxitin. Given concern for persistent immune deficiency, he was started on rituximab (375 mg/m^2 with doses at months 0, 1, 6, and 12). Amikacin, linezolid, and cefoxitin were added to his MAC regimen. Amikacin was stopped at 4 weeks due to nephrotoxicity

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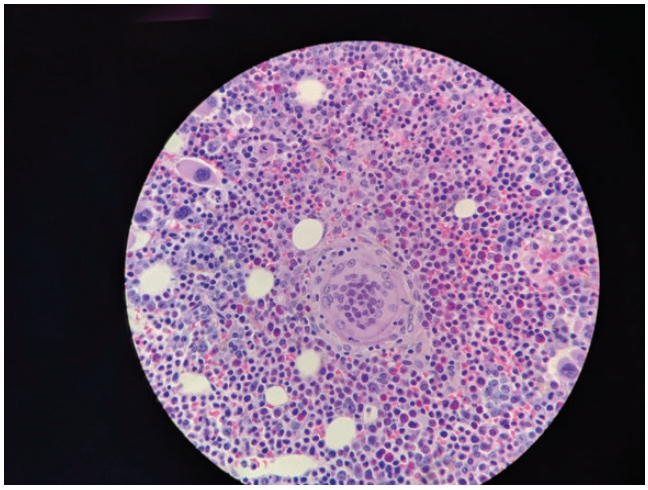

Figure 1. Hematoxylin and eosin stain demonstrating granuloma formation in bone marrow biopsy of a female with disseminated *Mycobacterium avium* complex infection.

and clofazimine added. Linezolid was discontinued after 4 months due to thrombocytopenia and cefoxitin stopped after 1 year. After 2 years of therapy, nIFNγ-autoAb dropped to half the previous level, and a CT scan showed resolution of disease, prompting discontinuation of therapy. In the subsequent

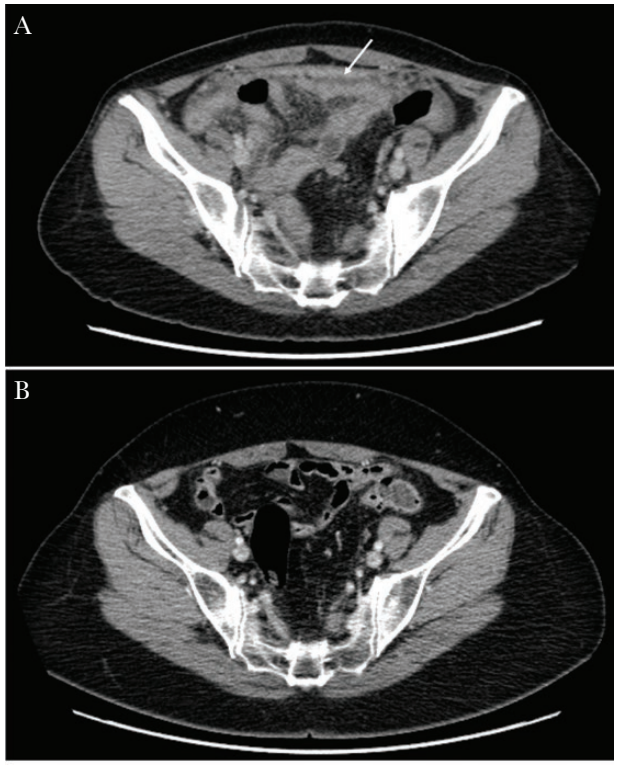

Figure 2. Axial views of abdominal computed tomography scan with contrast demonstrating omental caking (arrow) in a patient with intra-abdominal *Mycobacterium avium* complex infection before treatment (A) and 5 months after completion of therapy (B).

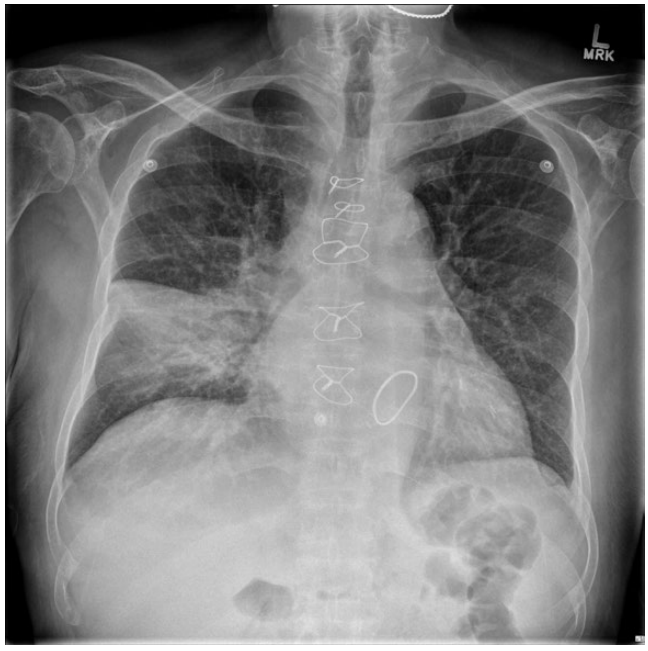

Figure 3. Chest radiograph demonstrating right lobar infiltrate in a patient with disseminated *Mycobacterium avium* complex infection with pulmonary involvement.

6 months, he had 1 episode of localized herpes zoster, but no evidence of mycobacterial disease.

Table 1 summarizes all 3 cases of dMAC with nIFNγ-autoAb.

DISCUSSION

Since its recognition in 2004, infectious complications of nIFN-γ autoAb have become an emerging concern worldwide [1, 2]. IFN-γ serves a critical role in linking myeloid and lymphoid immune pathways (Figure 4), promoting macrophage activation and differentiation [3]. Impairment of the IFN-γ pathway predisposes to viral (ie, CMV, VZV), bacterial (ie, *Mycobacterium* spp., *Salmonella* spp.), and fungal (ie, *Talaromyces* spp., *Histoplasma* spp., *Cryptococcus* spp.) infections, among which disseminated nontuberculous mycobacterium (dNTM) is the most commonly described [1, 2, 4, 5]. Despite a growing number of reported cases of dNTM with nIFN-γ autoAb, there is currently little guidance on treatment of these infections, a topic of particular importance given the complex and remitting nature of the disease. In this paper, we add to the accumulating evidence to support immunomodulatory therapies, review current treatment strategies, and propose a clinical approach to guide management.

Presentation and Diagnosis

These cases reflect many important features of dNTM in the setting of nIFN-γ autoAb. To date, 115 cases of dMAC with nIFN-γ autoAb have been reported, most of which presented with multifocal and advanced disease, typically involving the lymph nodes, lungs, and bone [1, 2, 6, 7]. Although autoantibodies to

Table 1. Demographic, Clinical, and Treatment Characteristics of 3 Cases of Disseminated *Mycobacterium avium* Complex With Neutralizing Interferon-Gamma Autoantibodies

	Patient 1	Patient 2	Patient 3
Age/gender	44 female	53 female	53 male
Ethnicity	Filipina	Cambodian	Filipino
Comorbidities	MCTD	GERD	T2DM
	HTN		Prior *Salmonella* spp. bacteremia
	GERD		Dyslipidemia
	Fatty liver		CAD
			HTN
			Atrial fibrillation
Duration of symptoms before diagnosis	5 mo	8 mo	12 mo
Disease extent	Lung, bone marrow, lymph node, liver	Lymph node, intra-abdominal	Lung, lymph node, bone, bloodstream
Immune workup			
HIV	Negative	Negative	Negative
CD4, CD8 subsets, absolute in μL (%)	CD4 – 380 (38)	CD4 – 500 (33)	CD4 – 360 (60)
	CD8 – 230 (23)	CD8 – 780 (52)	CD8 – 80 (13)
TB QFT	Indeterminate	-	Indeterminate
Initial nIFNγ-autoAb level (titer in fluorescent intensity; control titers ranging from 173 to 240)	19 071 (strongly positive)	19 934 (strongly positive)	18 278 (strongly positive)
Treatment & course			
Primary regimen	AZM, EMB, RFB	AZM, EMB, RIF	AZM, RFB, EMB, FOX, CFZ
Drugs discontinued due to toxicity	MXF	AMK	AMK, LZD, MXF
Course	Refractory to therapy	Refractory to therapy	Initial improvement then lymphadenopathy due to *M. abscessus*
	Rituximab added after 4 mo	Rituximab added after 3 mo	Rituximab initiated 10 mo after dMAC diagnosis
Duration of antimycobacterial therapy	24 mo	22 mo	24 mo
nIFNγ-autoAb titer after rituximab course (in fluorescent intensity)	11 350 (from 19 071 22 mo earlier)	Testing not performed	9131 (from 18 278 20 mo earlier)
Current status	Clinically well 6 mo after completing therapy	Clinically well 8 mo after completing therapy	Clinically well 6 mo after completing therapy

Abbreviations: AMK, amikacin; AZM, azithromycin; CAD, coronary artery disease; CFZ, clofazimine; EMB, ethambutol; FOX, cefoxitin; GERD, gastroesophageal reflux disease; HTN, hypertension; LZD, linezolid; MCTD, mixed connective tissue diseases; MXF, moxifloxacin; QFT, QuantiFERON-TB; RFB, rifabutin; RIF, rifampin; TB, tuberculosis.

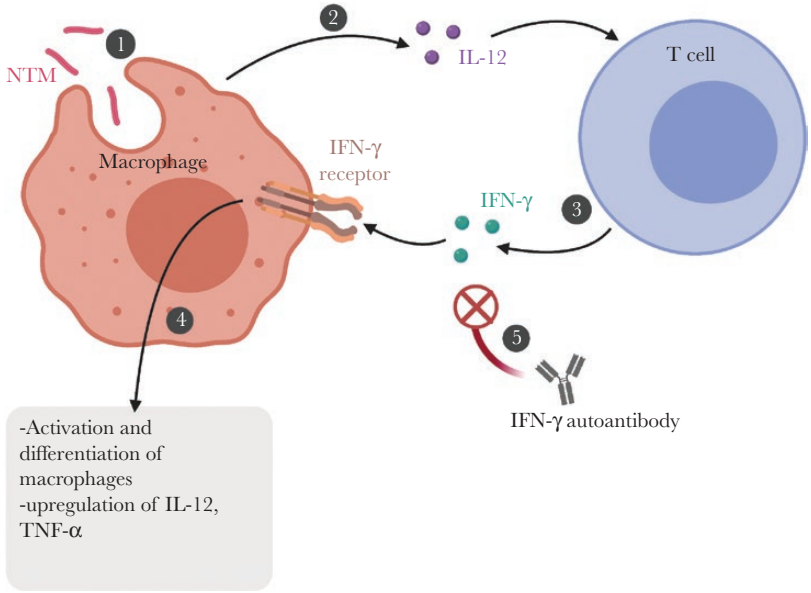

Figure 4. IFN-γ pathway: NTM and other intracellular pathogens are engulfed by macrophages (1) producing IL-12 (2), which goes on to stimulate natural killer or T-cell production of IFN-γ (3). IFN-γ promotes macrophage activation and differentiation, linking myeloid and lymphoid immunity pathways (4). IFN-γ autoantibodies act to bind and inactivate IFN-γ (5) [3]. Created with BioRender.com. Abbreviations: IFN, interferon; IL, interleukin; NTM, nontuberculous mycobacterium; TNF, tumor necrosis factor.

IFN-γ are predominantly seen in individuals of Southeast Asian descent, cases have also been reported in other ethnicities including Japanese [1], South African [8], British [8], German [9], and South Asian [10]. The predominant Southeast Asian representation likely relates in part to genetic HLA-polymorphisms common in this ethnicity (HLA-DRB1*16:02/DQB1*05:02) [6]. While our cases are the first Canadian cases described, this number will likely grow in areas with prominent Southeast Asian immigration as physicians become increasingly aware of this entity.

Diagnostic delay is common in dNTM with nIFN-γ autoAb. Our cases had symptoms for ~8 months before diagnosis, and all were initially diagnosed as tuberculosis (TB) or malignancy. Bias toward malignancy in particular can lead to delays if sample tissue is placed in formalin and sent only to pathology. The diagnostic gold standard for mycobacterial disease is culture, although rapid molecular methods such as polymerase chain reaction can distinguish between TB and MAC, most reliably on smear-positive samples [11, 12]. As these tests are limited by sensitivity, multiple clinical samples should be sent for culture to increase diagnostic yield [13].

The diagnosis of dNTM is unusual without an underlying immunodeficiency and warrants further interrogation. Clues suggestive of a cell-mediated immune defect include recurrent herpes zoster infections or disseminated salmonellosis, as was seen in Patient 3. In a recent case series from Taiwan of 45 patients with dNTM with nIFN-γ autoAb, 40% had a history of salmonellosis, 62% had herpes zoster, and 27% had both [14]. History of severe infections that rely on IFN-γ for clearance may be an important clue to its dysfunction. Box 1 outlines the suggested approach for a patient with suspected nIFN-γ autoAb.

In addition to ethnicity and recurrent infections, indeterminate QuantiFERON-TB testing (QFT) may also suggest the presence of nIFN-γ autoAb. QFT assays are contingent on release of IFN-γ from mononuclear cells in response to TB-specific antigens. The presence of nIFN-γ autoAb neutralizes any IFN-γ released, resulting in lack of mitogen response and yielding an indeterminate result. In both of our cases where testing was performed, an indeterminant QFT result served as an early clue to nIFN-γ autoAb presence. The role of indeterminant QFT testing as an early indicator of nIFN-γ autoAb is further supported by previous case reports [10, 15, 16] and a prospective study of HIV-negative patients with dNTM [17]. Here, Wu et al. demonstrated that 30 out of 30 patients with nIFN-γ autoAb had indeterminate QFT results due to extremely low or undetectable IFN-γ levels in the mitogen tubes, irrespective of nIFN-γ autoAb serum levels [17]. Thus, an indeterminate QFT test in an otherwise healthy patient with dNTM should prompt investigation for nIFN-γ autoAb, which may decrease diagnostic delay and prevent further invasive tests.

Natural History and Antimicrobial Therapy

As cases accrue, it is evident that the natural history of dNTM with nIFN-γ autoAb varies from that of other immunodeficiencies. In terms of dMAC with nIFN-γ autoAb, mortality is lower than dMAC in other immunocompromised states such as advanced HIV, even with available antiretroviral therapy (ART) [1]. In the largest studies of dNTM with nIFN-γ autoAb [1, 2, 4, 14, 18], the combined mortality rate was ~7% (18/269), compared with 29%–54% associated with HIV in the post-ART era [19, 20]. In contrast, relapse is more common in nIFN-γ autoAb–associated disease, occurring in up to two-thirds of cases, with drug-free remission rates as low as ~15% [1, 4, 14]. While mortality of dNTM with nIFN-γ autoAb is low, a relapsing course is common and poses challenges for long-term management.

Treatment of MAC depends on disease extent and host immune status but generally includes ≥12 months of combination antimicrobial therapy [13]. Few antibiotics have reliable activity against MAC, and in vitro susceptibility testing only consistently predicts activity for amikacin and clarithromycin. Similar to standard MAC regimens, most antibiotic regimens for nIFN-γ autoAb–associated dMAC included a macrolide, ethambutol, and rifamycin (Table 2) [1, 14, 21]. Other agents added included fluoroquinolones, oxazolidinones, clofazimine, amikacin, and carbapenems (Table 2). While optimal treatment duration remains unknown, treatment for nIFN-γ autoAb–associated cases reported in the literature has ranged from 18–31 months to as long as 7 years [1, 4, 14, 18]. Given extended treatment durations, macrolide resistance acquired as a result of prolonged therapy should always be considered in cases of recurrent disease, as this could have significant implications on long-term outcomes. Finally, the role of antimicrobial prophylaxis following therapy remains unknown and represents an important area for future research.

Rituximab Therapy for Refractory Cases

Rituximab is a monoclonal antibody against CD20 on B cells and has emerged as the most promising immune-modulating therapy for refractory nIFN-γ autoAb–associated infections [2, 18, 21–25]. Since its first use for such in 2012 [22], at least 21 cases of treatment with rituximab have been described to date [2, 21–25]. We summarize all cases with available clinical data (12 cases) to further delineate clinical and treatment characteristics (Table 2).

In all cases, rituximab was used in progressive disease despite long-term antimicrobial therapy. Time to rituximab addition varied from 3 to >12 months (Table 2). In most cases, there was improvement or lack of disease progression after initiation of rituximab, with the exception of 2 cases where disease course was more protracted, accompanied by a less robust reconstitution of IFN-γ [22, 26]. In 1 case, progression despite rituximab prompted the addition of daratumumab, a

Table 2. Reported Cases of Rituximab Treatment for Patients With Refractory Disseminated Nontuberculous Mycobacterial Infection With Neutralizing Interferon-γ Autoantibodies

First Author, Date (Ref)	Demographics	Microbiology	Disease Extent	Antimicrobial Therapy	Time From Diagnosis to Rituximab, mo	Response	Follow-up After First Rituximab Dose, mo	Rituximab Dosing Regimen (Duration of Therapy)
Browne, 2012 [7]	46 F Filipino	*M. abscessus*, MAC	LN, blood, urine, pelvic abscess, skin	CLR, EMB, INH, LZD, MXF, TGC[a]	>12	Improved[b]	5 y	375 mg/m^2 wkly × 4 doses, then at wider intervals, total 15 doses (3 y)
Browne, 2012 [7]	69 F Filipino	*M. abscessus*	LN, blood, bone	AMK, AMC, AZM, CIP, ETP, EMB, INH, LZD, MEM, PZA, RIF, TGC[a,c]	>12	Improved[b]	6 y	375 mg/m^2 wkly × 4 doses, then at wider intervals, total 18 doses (3 y)
Browne, 2012 [7]	50 F Laotian	MAC	LN, bone, muscle	CLR, EMB, MXF	>12	Improved[b]	4 y	375 mg/m^2 wkly × 4 doses, then at wider intervals, total 11 doses (1 y)
Browne, 2012 [7]	60 F Vietnamese	*M. intracellulaire*	Bone, muscle, skin	AMK, AZM, CLR, EMB, INH, LVX, MXF, PZA, RIF	>12	Initially protracted, then improved	2 y	375 mg/m^2 wkly × 4 doses, then at wider intervals, total 9 doses (2 y)
Czaja, 2014 [6]	78 M Japanese	*M. chelonae-abscessus*	LN, bone	AZM, IPM, TOB, MXF	9	Improved	8	375 mg/m^2 wkly × 4 doses (1 mo)
Naik, 2016 [18]	78 F Filipino	*M. abscessus*	Bone, blood	AMK, AZM, CIP, ETP, EMB, INH, LZD, MEM, PZA, RIF, TGC	NA	Improved	5 y	NA
Pruetpongpun, 2016 [16]	72 M Thai	*M. abscessus*, *Talaromyces marneffei*	LN, lung	INH, RIF, PZA, EMB, AMK, IPM, CLR, CIP	3	Improved	9	375 mg/m^2 wkly × 8 doses (2 mo)
Koizumi, 2017 [17]	67 F Japanese	MAC	Bone	RIF, CLR, EMB, STFX, AMK, LZD, AZM	7.5	Stopped progression	3	375 mg/m^2 wkly × 4 doses (1 mo)
Ochoa, 2020 [19]	31 F Filipino	MAC	Bone, LN, soft tissue	AZM, EMB, MXF, CFZ, MEM, TZD, BDQ	NA	Progression at 6 mo with improvement after initiation of daratumumab	NA	1 g monthly × 5 mo
Our case	44 F Filipino	MAC	LN, BM, lung, liver	AZM, EMB, RFB, MXF	4	Improved	27	375 mg/m^2 monthly × 2 doses (2 mo)
Our case	53 F Cambodian	MAC	LN, intra-abdominal	AZM, RIF, AMK, MXF	3	Improved	28	375 mg/m^2 wkly × 4 doses every 3 mo, total 16 doses (9 mo)
Our case	53 M Filipino	MAC, *M. abscessus*	LN, lung, bone	AZM, RFB, EMB, MXF, AMK, CFZ, FOX, LZD	10	Improved	20	375 mg/m^2 monthly at 0, 1, 6, 12 mo (12 mo)

Abbreviations: AMC, amoxicillin-clavulanic acid; AMK, amikacin; AZM, azithromycin; BDQ, bedaquiline; BM, bone marrow; CFZ, clofazimine; CIP, ciprofloxacin; CLR, clarithromycin; EMB, ethambutol; ETP, ertapenem; FOX, cefoxitin; IFN, interferon; INH, isoniazid; LN, lymph node; LVX, levofloxacin; LZD, linezolid; MAC, *M. avium* complex; MEM, meropenem; MXF, moxifloxacin; PZA, pyrazinamide; RFB, rifabutin; RIF, rifampin; STFX, sitafloxacin; TOB, tobramycin; TGC, tigecycline; TZD, tedizolid.

[a]Treatment included IFN-γ infusion.

[b]Relapse occurred with retreatment and clinical improvement.

[c]Treatment included plasmapheresis.

monoclonal antibody targeting CD38 on multiple immune cells, with subsequent clinical improvement [26]. In cases that responded to rituximab, clinical response occurred ~2 months after initiation [22, 23], but has been reported to occur as early as 10 days [24] and as late as 6 months into therapy [22]. As a whole, the significant improvement seen in the majority of these cases including ours, suggests that rituximab is a promising adjunct in some of the most challenging and refractory cases.

With increasing evidence of effectiveness, there is an urgent need to determine optimal rituximab dosing. The majority of nIFN-γ autoAb cases used a dose of 375 mg/m^2 initially at

weekly dosing intervals, similar to that used in lymphoma (Table 2) [22]. In 1 case of disease that progressed after rituximab treatment, a monthly regimen was used, resulting in a lower cumulative dose. It remains unclear whether increased dosing frequency may have improved response in this case [26]. In our cases, dosing frequency varied considerably due to individual disease burden and health insurance coverage. We saw equally excellent treatment outcomes with a variety of dosing regimens, suggesting that an immune response may be seen after only a few rituximab doses in some individuals.

Clinical, microbiologic, and radiographic assessment are essential to establishing therapeutic response when managing NTM. In some cases, nIFN-γ autoAb levels have additionally been used to monitor response to rituximab [24]. IFN-γ autoAb levels may drop by 30%–40% as early as 4 weeks after rituximab therapy, and antibody-depleting effects can persist for months [21, 22, 24]. Relapse following discontinuation of rituximab therapy was reported in 3 cases, each associated with increased nIFN-γ autoAb levels, suggesting that antibody levels may augment clinical evaluation as a predictor for recurrent disease [22]. For our cases, nIFN-γ autoAb testing is not available in commercial assays in Canada, and autoAb levels were measured by particle-based multiplex assays [2] at a National Institutes of Health research lab in the United States. Because of this, serial testing is limited by cost and turnaround time. For 2 patients, end-of-therapy nIFN-γ autoAb titers were measured and were decreased but not normalized, suggesting the ongoing need for close monitoring of these patients.

Other Immunomodulatory Therapy for nIFN-γ AutoAb

Other immunomodulating therapies have been used for refractory disease with varying success. In a review of various treatments, adjunct therapies such as IFN-γ infusions (n = 5), intravenous immunoglobulin (n = 3), and plasmapheresis (n = 1) showed no consistent improvement in refractory disease [27]. The role of cyclophosphamide, a T- and B-cell-depleting agent, has been used successfully in several cases [28, 29]. In a pilot study comparing cyclophosphamide (n = 11) with rituximab (n = 6) for IFN-γ autoAb–associated disease, there was no significant difference in partial or full remission at 6 months between the groups, and those receiving cyclophosphamide had faster and more durable remission [30]. This pilot suggests that cyclophosphamide may be used as an immunomodulatory alternative particularly when access to rituximab is limited. Finally, immunomodulatory therapies generally reserved for hematologic malignancies have also prompted new interest. In a recent case report, R-CHOP (rituximab - cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy was successfully used to treat dMAC with nIFN-γ autoAb, a regimen that was given for lymphoma but resulted in resolution of dMAC hepatic abscesses [31]. Similarly, daratumumab, a monoclonal antibody used in the treatment of multiple myeloma, successfully treated nIFN-γ autoAb–associated disease that was refractory to rituximab [26]. While many of these therapies and their side effects warrant further investigation, together they underscore the growing recognition of immunotherapy as a cornerstone of treating dMAC with nIFN-γ autoAb.

CONCLUSIONS

Herein, we present 3 cases of refractory dMAC with nIFN-γ autoAb to illustrate the complexity of disease and propose a framework to guide management (Box 1). Clinicians should suspect underlying nIFN-γ autoAb in otherwise healthy Southeast Asian patients who develop dNTM infections. Management is challenging, requiring long-term antibiotic regimens, and rituximab holds promise for the treatment of refractory disease.

BOX 1. SUGGESTED APPROACH TO DIAGNOSIS AND MANAGEMENT OF dMAC ASSOCIATED WITH nIFN-γ AUTOAB

Clinicians should suspect possible nIFN-γ autoAb in otherwise healthy patients with dMAC and the following:

- Southeast Asian heritage
- Negative HIV1/2 testing
- Prior or recurrent severe infections involving the IFN-γ pathway:
  - Viral (CMV, VZV)
  - Bacterial (*Mycobacterium* spp., *Salmonella* spp.)
  - Fungal (*Talaromyces* spp., *Histoplasma* spp., *Cryptococcus* spp.)
- Indeterminate QuantiFERON-TB (QFT) result
- No alternate explanation for dMAC (ie, other inherited or acquired immune deficiencies)

Initial antimicrobial therapy should include:

- Macrolide (clarithromycin or azithromycin)
- Ethambutol
- Rifamycin

Further consideration of additional antimicrobials should be based on resistance patterns, refractory disease, or drug intolerance.

Management of refractory/recurrent disease:

- Immunomodulatory therapies such as rituximab should be considered
- Rituximab is generally dosed at 375 mg/m^2. The ideal dosing interval/duration requires further study. Most collective experience is with a regimen of weekly dosing for at least 4 weeks.
- Monitoring should by clinical, microbiologic, and radiographic follow-up. nIFN- γ autoAb or pSTAT1-alpha levels could be measured serially to assess disease activity when available.

As nIFN-γ autoAb–related infections continue to emerge worldwide, further investigation of long-term management of this entity will be important.

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Author contributions. Report conception (E.M.K., V.K.W., M.H.K.), chart reviews (E.M.K., V.K.W.), data collection (E.M.K., V.K.W.), literature review (E.M.K., V.K.W.), drafting the manuscript (E.M.K., V.K.W.), and revision of the manuscript (E.M.K., V.K.W., M.H.K.). All authors approved the submitted manuscript version and have agreed to be personally accountable for any questions related to the accuracy or integrity of any part of the work.

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