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Case report

The chicken and the egg dilemma: A case of disseminated MAC with Hodgkin's lymphoma

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ABSTRACT

Introduction: Mycobacterium avium complex (MAC) as a cause of disseminated disease has been well described in immunocompromised hosts. We report a case of disseminated MAC diagnosed in an otherwise healthy patient, one year before further testing and follow-up revealed a diagnosis of Hodgkin's lymphoma.

Case presentation: A 48-year-old woman with no significant medical history presented with new-onset fever, chills and night sweats. Chest imaging revealed large conglomerate mediastinal lymph nodes (LN). Endobronchial ultrasound-guided biopsy demonstrated caseating granulomatous inflammation and MAC on broth culture. She was started on guideline-based antibiotic therapy for disseminated MAC but showed no improvement after 6 months. An open mediastinal biopsy confirmed the findings of non-caseating granuloma. However, due to continued symptoms and widespread lymphadenopathy on additional full body imaging, an iliac lymph node core biopsy was performed which revealed abnormal $CD30^{+}$ lymphoid infiltrate consistent with Hodgkin's lymphoma (HL). She was started on steroids and chemotherapy, whilst maintained on MAC treatment.

Discussion: Disseminated MAC is largely limited to immunocompromised hosts, signs and symptoms of which may overlap with lymphoma. Our case demonstrated that multiple initial LN biopsies were unrevealing except for MAC. As no clinical improvement was observed with guideline based MAC treatment, further diagnostic measures were aggressively pursued ultimately leading to a diagnosis of HL. It is unclear whether disseminated MAC preceded lymphoma, an early undiagnosed lymphoma led to MAC infection or an undefined systemic immune disorder was causative for both these processes.

1. Background

Mycobacterium Avium Complex (MAC) is the most common non-tuberculous mycobacterial species associated with human disease. While the main portal of entry is unknown, evidence suggests that pulmonary disease may occur through inhalation of infected airborne particles, becoming the crucial primary step for systemic involvement in a subset of cases [1]. As MAC related pulmonary disease has become increasingly common, disseminated disease has declined over recent decades. Previously, disseminated MAC was well-described in Acquired Immunodeficiency Syndrome (AIDS) [2], but with the advent of highly active antiretroviral therapy (HAART) this has become much less common in this cohort. Still, MAC infection remains problematic in other patients with compromised immunity, as one recent study found 46 of 105 NTM patients on immunosuppressive therapy had disseminated disease [2]. While data is limited, there are several reports of coexistent Hodgkin's lymphoma and Tuberculosis (TB) in the literature, and some reported cases of concomitant MAC infection and Epstein -Barr virus (EBV)-associated Hodgkin's with AIDS [3,4]. These cases highlight the generally accepted pathophysiology that lymphoma renders an individual immunologically vulnerable and thereby susceptible to an opportunistic infection like disseminated MAC. We present this case of disseminated MAC, in a chronically symptomatic patient, which preceded a diagnosis of lymphoma by one calendar year.

2. Case report

A 48-year-old woman with no significant past medical history apart from elective bilateral breast implantation 10 years prior, presented with new onset of fever, rigors, night sweats and shortness of breath. Initial workup revealed microcytic anemia (Hb 8.9 g/dL, MCV 78 fL leukopenia and elevated CRP 143 mg/dL and ESR >130 mm/h). Chest CT scan revealed 3 cm pericardial effusion with large conglomerate mediastinal lymph nodes (LN) and scant tree-in-bud opacities on lung

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images. She underwent pericardiocentesis and transthoracic paratracheal LN biopsy which were negative for infection or malignancy.

Due to progressive cough, fatigue, night sweats and weight loss further diagnostic testing including bronchoscopy and endobronchial ultrasound (EBUS) were performed. Fine needle aspirates (FNA) demonstrated caseating granulomatous inflammation with growth of MAC on broth culture but no evidence of malignancy. Interferon gamma release assay was negative and sputum with PCR for *mycobacterium tuberculosis*, were all negative. Subsequently, one of three sputum cultures grew MAC (broth) but all other microbiologic cultures remained negative. Additional testing for alternative infectious etiologies including HIV, syphilis, cytomegalovirus, toxoplasma, aspergillus, cryptococcus and histoplasma were negative. She underwent further LN assessment via mediastinoscopy which again revealed caseating granulomatous inflammation and growth of MAC (broth). Flow cytometry, performed on EBUS and mediastinoscopy samples were negative for malignancy.

Based on the finding of MAC on two separate LN cultures and biopsy finding of non-caseating granuloma, with no alternative diagnosis, she was started on daily triple antibiotic therapy with Ethambutol 1200 mg, Azithromycin 500 mg and Rifampin 600 mg. However, she failed to demonstrate any improvement in her clinical condition after 6 months of therapy. Further diagnostic testing inclusive of a bone marrow biopsy returned negative for malignancy. Repeat whole body CT imaging demonstrated widespread lymphadenopathy along with a new right ovarian mass. An extensive workup focused on evaluation for underlying malignancies or secondary immunodeficiencies was carried out. CA-125, CA19-9, CEA biomarkers were normal, LDH levels remained <200 U/L. Gynecology was consulted for the ovarian mass which was determined to be benign. Further immunologic evaluation demonstrated low CD3, CD4 and CD56 levels. A rheumatology profile including ANA, extended autoimmune panel, rheumatoid factor, vasculitis panel, *anti*-CCP were all within normal limits. Ultimately, a core biopsy of an iliac LN demonstrated abnormal CD30-positive lymphoid infiltrate, suspicious for Hodgkin's lymphoma (HL). An excisional left supraclavicular lymph node biopsy was performed, confirming the diagnosis of Hodgkin's lymphoma along with histologic evidence of granulomatous inflammation and AFB smear positivity.

The subject was started on steroids followed by initiation of chemotherapy whilst being maintained on MAC treatment with Ethambutol and Azithromycin three times a week. Rifampin had to be discontinued due to persistent leukopenia. The patient tolerated chemotherapy well with symptomatic improvement, however an interim Positron Emission Tomography (PET)/CT scan revealed residual disease with widespread hypermetabolic lymphadenopathy involving the neck, mediastinum, and abdomen. The chemotherapeutic regimen was subsequently escalated and follow-up PET/CT scan demonstrating overall decrease in the tumor volumetric activity with minimal disease relating to either residual MAC/granulomatous inflammation or Hodgkin's disease. A repeat excisional biopsy of cervical LNs was negative for lymphoma but revealed necrotizing granuloma with negative AFB cultures Patient is currently doing well on continued suppressive MAC treatment with Ethambutol and Azithromycin while undergoing close surveillance for any recurrence of her lymphoma.

3. Discussion

MAC is an important pathogen for opportunistic infection in the immune-suppressed host, with high risk for dissemination, due to an innate ability to subvert host defenses [1]. Disseminated MAC has been well described in susceptible hosts, including, but not limited to bone marrow transplantation recipients, patients on immunosuppressive chemotherapy and people living with AIDS [5]. It is known is that mixed T-cell and B-cell mediated immune defects occur in Hodgkin's lymphoma conferring immunologic vulnerability. Similarly, the pathogenesis of mycobacterial infections in advanced lymphomas is complex and includes both humoral and cellular immune dysfunction along with cumulative immunosuppression related to lymphoma treatment [6]. Inherent immunological dysfunction involving T-cells, NK cells, dendritic cells, phagocytes and complement have been studied as causal factors of MAC associated lymphadenitis in CLL with no prior treatment [6,7]. However, the precise impact of these immunological defects on risk of infection in lymphomas and their reversibility after treatment has been difficult to quantify.

Conversely, our case illustrates disseminated MAC, in an otherwise healthy host, found to have HL one year after her MAC diagnosis. One may opine that this was a coincidental occurrence, with no causal association between MAC and HL. There is no data to suggest that MAC can lead to HL. It would stand to reason that HL could predispose to disseminated MAC, but in our patient, multiple LN sampling techniques failed to demonstrate evidence of malignancy at the time of MAC diagnosis making the contribution of sampling error unlikely.

From a diagnostic standpoint, fine needle aspirates do not provide adequate amounts of material for proper histologic classification nor molecular studies needed in the evaluation of lymphomas. The diagnosis of HL is typically established by histologic, immunologic and molecular examination of an excised lymph node demonstrating "classic" Hodgkin/Reed-Sternberg cells. These malignant cells may represent only a minority (<1%) of the cellular infiltrates, explaining why the diagnosis may be missed on simple FNA [8]. The diagnostic sensitivity of excisional LN biopsies for lymphoma, range from 80 to 100% and from 72 to 100% for core needle biopsies (CNB). On the contrary, the sensitivity of FNA ranges broadly from 12% to 82% [9,10]. Due to these limitations, the average time to diagnose lymphoma varies from 2.5 months to one year [11]. BM aspirates alone are of low yield and are often negative even when the bone marrow is involved, due to the presence of lymphoma-induced fibrosis [12]. However, LN and BM biopsies are sensitive for detection of caseating granulomas, a common histologic finding for diagnosis of disseminated mycobacterial infection. The sensitivity of mycobacterial culture from LN biopsies may vary depending on whether the lymph node is caseous and is ~17% for FNA culture and 40–60% for excisional LN biopsies. The diagnostic sensitivity of BM histopathology in the diagnosis of MAC as reported by various studies is 20–30% [13,14].

In this case, MAC was isolated from a mediastinal LN FNA as well as from one of the early sputum cultures. Our patient underwent multiple LN sampling procedures (transthoracic, EBUS, mediastinoscopy) at the onset of symptoms. While it is possible the diagnosis of HL was initially missed due to inadequate sampling, the diagnostic pathway overwhelmingly supports that the initial diagnosis of disseminated MAC preceded the detection of HL one year later. Clinically, our patient had presented with fever, night sweats, and weight loss which persisted, and progressed over several months. These symptoms, present in individuals with disseminated MAC, also overlap with the typical B-symptoms associated with Hodgkin's lymphoma. Commonly identified, but nonspecific laboratory abnormalities of both disseminated MAC and lymphoma include anemia, neutropenia and elevated inflammatory markers, were also observed in this patient.

Therefore, this case report outlines two distinctive pathologies that may present with similar signs and symptoms. In our patient, the infection preceded the finding of HL by a year. This poses an interesting immunologic conundrum of whether a primary immune defect, yet undetected, predisposed to the subsequent sequelae of disseminated MAC and finally HL.

4. Conclusion

This case highlights the need for clinicians to be aware of the similarity in clinical presentation of disseminated MAC infection and systemic malignancies like lymphoma. Further, it is simultaneously unique, and intriguing, that disseminated MAC developed prior to malignancy in an otherwise healthy individual. We emphasize the importance of an

aggressive work up, inclusive of LN FNA, but also excisional LN biopsy if initial findings and outcome parameters are not conclusive and the response to MAC-targeted treatment is inadequate.

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Credit author statement

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Declaration of competing interest

The authors have no significant conflict of interests to report.

References

[1] K.L. Winthrop, E. McNelley, B. Kendall, A. Marshall-Olson, C. Morris, M. Cassidy, A. Saulson, K. Hedberg, Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease, Am. J. Respir. Crit. Care Med. 182 (7) (2010) 977–982.

[2] C.H. Chou, H.Y. Chen, C.Y. Chen, C.T. Huang, C.C. Lai, P.R. Hsueh, Clinical features and outcomes of disseminated infections caused by non-tuberculous mycobacteria in a university hospital in Taiwan, 2004-2008, Scand. J. Infect. Dis. 43 (1) (2011) 8–14.

[3] Y. de Armas, V. Capo, I. Gonzalez, L. Mederos, R. Diaz, J.H. de Waard, A. Rodriguez, Y. Garcia, R. Cabanas, Concomitant Mycobacterium avium infection and Hodgkin's disease in a lymph node from an HIV-negative child, Pathol. Oncol. Res. 17 (1) (2011) 139–140.

[4] P. Brousset, B. Marchou, S.M. Chittal, G. Delsol, Concomitant Mycobacterium avium complex infection and Epstein-Barr virus associated Hodgkin's disease in a lymph node from a patient with AIDS, Histopathology 24 (6) (1994) 586–588.

[5] R. Kurzrock, L. Vellekoop, M. Kanojia, M. Luna, K. Dicke, A. Zander, Mycobacterial pulmonary infections after allogeneic bone-marrow transplantation, Am. J. Med. 77 (1) (1984) 35–40.

[6] S. Tsiodras, G. Samonis, M.J. Keating, D.P. Kontoyiannis, Infection and immunity in chronic lymphocytic leukemia, Mayo Clin. Proc. 75 (10) (2000) 1039–1054.

[7] B.W. Teh, C.S. Tam, S. Handunnetti, L.J. Worth, M.A. Slavin, Infections in patients with chronic lymphocytic leukaemia: mitigating risk in the era of targeted therapies, Blood Rev. 32 (6) (2018) 499–507.

[8] D.A. Bowen, K.G. Rabe, S.M. Schwager, S.L. Slager, T.G. Call, D.S. Viswanatha, C. S. Zent, Infectious lymphadenitis in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma: a rare, but important, complication, Leuk. Lymphoma 56 (2) (2015) 311–314.

[9] W.A. Lachar, I. Shahab, A.J. Saad, Accuracy and cost-effectiveness of core needle biopsy in the evaluation of suspected lymphoma: a study of 101 cases, Arch. Pathol. Lab Med. 131 (7) (2007) 1033–1039.

[10] E. Ravinsky, C. Morales, Diagnosis of lymphoma by image-guided needle biopsies: fine needle aspiration biopsy, core biopsy or both? Acta Cytol. 49 (1) (2005) 51–57.

[11] D.A. Howell, A.G. Smith, A. Jack, R. Patmore, U. Macleod, E. Mironska, E. Roman, Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network, BMC Hematol 13 (1) (2013) 9.

[12] R.S. Stein, J.E. Ultmann, G.E. Byrne Jr., E.M. Moran, H.M. Golomb, N. Oetzel, Bone marrow involvement in non-Hodgkin's lymphoma: implications for staging and therapy, Cancer 37 (2) (1976) 629–636.

[13] J.M. Kilby, M.B. Marques, D.L. Jaye, P.B. Tabereaux, V.B. Reddy, K.B. Waites, The yield of bone marrow biopsy and culture compared with blood culture in the evaluation of HIV-infected patients for mycobacterial and fungal infections, Am. J. Med. 104 (2) (1998) 123–128.

[14] J.M. Fontanilla, A. Barnes, C.F. von Reyn, Current diagnosis and management of peripheral tuberculous lymphadenitis, Clin. Infect. Dis. 53 (6) (2011) 555–562.