Case report

Castleman flare or COPD exacerbation— can biomarkers override availability bias?

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ABSTRACT

Effective treatments for human herpes virus 8 (HHV-8) associated multicentric Castleman disease (MCD) have led to prolonged survival for this complex systemic lymphoproliferative inflammatory disease. Nonetheless, significant challenges remain for the recognition of disease exacerbations, particularly when overlapping with common comorbid conditions. We present a case of a 60-year-old man with a 22-year history of MCD, current advanced COPD, and medication-controlled HIV. His recurrent presentations with flares of fatigue, worsening dyspnea, and productive cough were confusing to clinicians who were attempting to distinguish between exacerbations of MCD or COPD. Published biomarkers of MCD flare include HHV-8 and CRP, which were proposed by the patient to his clinicians as useful in guiding treatment. This case illustrates the value of patient insight as an antidote to the problem of availability bias.

1. Introduction

1.1. Castleman disease

Castleman disease (CD) describes a number of rare lymphoproliferative disorders with similar histopathologic features [1,2]. Multicentric CD (MCD) is typically characterized by diffuse lymphadenopathy with associated systemic inflammatory response. MCD has two broadly recognized subtypes: human herpes virus 8 (HHV-8)-associated and not HHV-8-associated MCD.

The pathophysiology and symptomatic sequela of MCD have been linked with excess IL-6 production by B-lymphocytes in CD germinal centers, resulting in B-lymphocyte hyperplasia, lymph node vascular proliferation, and significant inflammatory response [3,4].

HHV-associated CD is most commonly multicentric, with pathophysiology thought to be due to unregulated HHV-8 proliferation in B-lymphocytes [4,5]. Historically, the median survival of HIV-associated CD was less than 25 months, though this is improving with recent therapeutic advancements [4].

There have been no randomized clinical trials on the management and treatment of MCD [4]. Treatment for MCD exacerbations most commonly entails high-dose steroids and rituximab or an alkylating agent, with success reported in a number of case reports [4].

1.2. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by impaired pulmonary function, dyspnea, and decreased quality of life [6]. Current classification and associated treatment guidelines are delineated not only by forced expiratory volume in the first second of expiration (FEV1), but also symptom burden and exacerbation history [7]. FEV1 provides a poor model for exacerbation status [6]. The mainstay of COPD exacerbation treatment has been antibiotics and steroids [8].

1.3. Use of biomarkers in these diseases

Over the last decade, biomarkers have become increasingly researched in an attempt to better diagnose various disease states, including MCD and COPD exacerbations.

In MCD, high HHV-8 viral load is commonly found in peripheral blood mononuclear cells, as detected by quantitative polymerase chain reaction, which directly correlates with MCD exacerbations [4,9,10]. In addition to HHV-8 viral load, IL-6, IL-10, and CRP have been noted to correlate with exacerbation of HIV-associated MCD [10]. While this is well documented in the literature, it is not broadly clinically recognized nor applied.
In a systematic review performed by Chen et al. to identify promising biomarkers in COPD exacerbations, the most studied biomarkers in the 59 studies included were CRP, IL-6 and TNF-α. While CRP showed consistent elevations in COPD exacerbations as compared to controls, IL-6 and TNF-α levels showed variable reliability [6]. A standardized approach to biomarker use in diagnosis and management of COPD has yet to be drafted.

2. Case presentation

The patient is a 60-year-old man with HHV-8 associated MCD, HIV/AIDS, and COPD (GOLD stage 4D) with a 40 pack-year smoking history. His HIV has been well-treated since 1996, with an undetectable viral load and CD-4 >500 cells/mm³. In 1998, he developed worsening fatigue, fevers to 41 °C, night sweats, rigors, anorexia, and generalized lymphadenopathy. A biopsy-confirmed diagnosis of HHV-8 associated MCD was made following nine months of relapsing-remitting symptomatology [11]. The patient has previously participated in clinical trials, but recently has received rituximab therapy initiated at the time of exacerbations.

Over the last decade, the patient’s respiratory status deteriorated. Pulmonary function tests documented a FEV1 of 30% predicted in 2011 on treatment with a short-acting muscarinic agonist and short-acting beta agonist, to a nadir of 19% predicted in 2018 with gradual escalation of treatment to a long-acting muscarinic agonist, long-acting beta agonist, and inhaled corticosteroid. Outpatient disease monitoring included PFTs, HIV viral load, and CD4 count.

The patient was hospitalized nine times between 2006 and 2019 at the same academic medical center for acute illness with predominant respiratory symptoms. Clinically, it was challenging to distinguish between COPD exacerbations and MCD flares for this patient. Computed tomography findings demonstrated airflow thickening and progressive hyperinflation, but did not assist in identifying the cause of his symptoms. His exacerbated COPD symptoms include dyspnea and cough with modestly increased sputum production with an acute onset over several days. His MCD flares are characterized by an insidious onset over months of profound dyspnea, night sweats, and cough with significantly increased, very viscous, tenacious phlegm. His diagnosis, while often clear to him, was less frequently clear to his providers. Given the significant overlap in symptomatology between COPD and MCD for this patient, these acute illnesses were often attributed to a COPD exacerbation, as respiratory symptoms are less common in MCD flares.

Hoping to persuade his treating clinicians of his perception that he was heading into an MCD flare, he provided medical literature supporting HHV-8 viral load and CRP as reliable biomarkers of MCD exacerbation and brought to clinic visits his hand-plotted graphs of past laboratory results performed over the years of his illness. As his symptoms flared, the patient would request monitoring of HHV-8 viral load over the years of his illness. As his symptoms flared, the patient would request monitoring of HHV-8 viral load and CRP. See Fig. 1 showing close correlation of the patient’s HHV-8 viral load, CRP values, and response to rituximab treatment and Fig. 2 demonstrating close correlation of measured HHV-8 viral load to CRP. His clinicians were aware that CRP is seen to be elevated in acute exacerbations of COPD, but were uncertain as to the possible interplay between MCD, HHV-8 viral load, and COPD.

Even as his outpatient physicians measured rising HHV-8 viral load and his MCD symptoms worsened to the point that he sought hospitalization, his inpatient physicians were impressed by his advanced COPD and were reluctant to initiate MCD treatment with rituximab. Rather, they began by treating for an acute exacerbation of COPD with antibiotics and oral steroids. In the interval between the patient recognizing the onset of an MCD flare, biomarker rising, and clinician willingness to initiate MCD therapy, the patient had unrelenting symptoms and prolonged inpatient stays with COPD exacerbation treatment.

3. Discussion

3.1. Treatment of MCD versus COPD

This case demonstrates the importance of distinguishing between MCD and COPD, because in this patient, treatment with rituximab in the setting of an exacerbation alleviated his MCD symptoms, whereas treatment for COPD (with steroids and antibiotics alone) did not. Given this dilemma, biomarkers with improved specificity would be especially useful.

3.2. Exacerbations of MCD and COPD

Both MCD and COPD are associated with exacerbations. MCD exacerbations typically include primarily constitutional symptoms such as fever, night sweats, weakness, fatigue, and anorexia, often accompanied by weight loss [4]. Conversely, COPD exacerbations typically involve increased cough, worsening dyspnea, wheezing, and increased sputum production [5]. The multifactorial etiology of his respiratory deterioration includes his former smoking and current HIV status.

Our suspicion was earlier treatment with rituximab might have had an added benefit of aiding in preventing some of this patient’s COPD exacerbations. The patient would identify a month’s long worsening of symptoms that he associated with MCD, with associated rise in measured HHV-8 viral load. This slow rise in symptoms preceded an acute exacerbation of COPD and its treatment with immunosuppression. For this reason, we think it unlikely that a COPD exacerbation and its treatment with immunosuppression caused the preceding HHV-8 viral load rise. It is plausible that the increased HHV-8 viral load may have caused the COPD exacerbation. It is also possible that the
proinflammatory, cytokine-mediated state of an MCD exacerbation contributed to worsening of his COPD, independent of the HHV-8 viral load.

In this patient, who had an unusually long disease course, we have the opportunity to compare the specific characteristics of his exacerbations in both of these conditions. While in-hospital clinicians encountering him for the first time were often confused as to which condition was responsible for his symptoms at a given time, he had a strong sense of which of these two conditions was destabilized.

3.3. Diagnostic decision-making conundrum

While providers can accurately diagnose a common disease more than half of the time, rare diseases or rare presentations of common diseases of are diagnosed accurately less than 5% of the time [12]. Availability bias, or the tendency to reach for the common diagnosis [12], was likely at play in this patient’s case. When presenting to the hospital with worsening dyspnea, increased sputum production, and constitutional symptoms, inpatient clinicians repeatedly attributed his symptoms to a COPD exacerbation and proposed antibiotics and steroids as first-line treatment. However, the symptom cluster was familiar to this patient as an MCD flare. In addition, recognizing that it had been almost one year since his last rituximab infusion, the patient felt strongly that MCD was the culprit and advocated for the use of biomarkers to aid clinicians in reaching the same conclusion.

4. Conclusion

Identifying the etiology of acute exacerbations of disease can be challenging in patients with poly-morbidity, particularly in the absence of specific biomarkers. The patient herein has extraordinary longevity when compared with the mean survival of his disease. Given this fact, in addition to the rarity and pleomorphic nature of MCD presentations, many of his treating clinicians found themselves in unfamiliar waters with availability bias leading to a propensity to diagnose the more common condition, COPD. This patient’s familiarity with his disease, along with his health literacy and self-advocacy lead to him providing valuable guidance to clinicians, including his longitudinal biomarkers tracked across multiple health systems. This case illustrates how a patient with a rare disease can provide valuable longitudinal clinical information to assist their clinicians with differential diagnosis and disease management.

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Benjamin B. Claxton: Writing - original draft, Data curation, Formal analysis.
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