Impact of a Multidisciplinary Tumor Board on the Care of Patients with Histiocytic Disorders: The Histiocytosis Working Group experience

Gaurav Goyal1,2,∗, Jason R. Young3, Jithma P Abeykoon2, Mithun V. Shah2, N. Nora Bennani2, Julio C Sartori-Valinotti4, Robert Vassallo5, Jay H. Ryu5, W. Oliver Tobin6, Matthew J. Koster7, Caroline J. David-Pitts8, Aishwarya Ravindran9, Karen L. Rech9, Ronald S. Go2,∗, on behalf of the Mayo Clinic-University of Alabama at Birmingham Histiocytosis Working Group

1Division of Hematology-Oncology, University of Alabama at Birmingham, Birmingham, AL, USA
2Division of Hematology, Mayo Clinic, Rochester, MN, USA
3Department of Radiology, Mayo Clinic, Rochester, MN, USA
4Department of Dermatology, Mayo Clinic, Rochester, MN, USA
5Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
6Department of Neurology, Mayo Clinic, Rochester, MN, USA
7Department of Rheumatology, Mayo Clinic, Rochester, MN, USA
8Division of Endocrinology, Diabetes, and Nutrition, Mayo Clinic, Rochester, MN, USA
9Division of Hematopathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

∗Corresponding authors: Ronald S. Go, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA; Tel: +1 507 284 5362; Email: go.ronald@mayo.edu; Gaurav Goyal, University of Alabama at Birmingham, 1802 6th Avenue South Suite 2555 NP, Birmingham, AL-35294, USA; Tel: +1 205 934 6770; Email: ggoyal@uabmc.edu

Abstract

Introduction: Histiocytic disorders pose significant diagnostic and management challenges for the clinicians due to diverse clinical manifestations and often non-specific histopathologic findings. Herein, we report the tumor board experience from the first-of-its-kind Histiocytosis Working Group (HWG).

Materials and Methods: The HWG was established in June 2017 and consists of experts from 10 subspecialties that discuss cases in a multidisciplinary format. We present the outcome of tumor board case discussions during the first 2 years since its inception (June 2017-June 2019).

Results: Forty cases with a suspected histiocytic disorder were reviewed at HWG during this time period. Average number of subspecialties involved in HWG case discussion was 5 (range, 2-9). Histiocytosis Working Group tumor board recommendations led to significant changes in the care of 24 (60%) patients. These included change in diagnosis (n=11, 27%) and change in treatment (n=13, 33%).

Conclusion: Our report highlights the feasibility of a multidisciplinary tumor board and its impact on outcomes of patients with histiocytic disorders.

Key words: Erdheim–Chester disease, immunoglobulin G4-related disease, histiocytes, osteopoikilosis, giant cell tumor of tendon sheath.

Implications for Practice

Patients with histiocytic disorders often suffer from delays in diagnosis and misdiagnosis due to the complex disease presentations. This article reports the outcomes of case discussions from a multidisciplinary tumor board (Histiocytosis Working Group) and highlights the feasibility of this approach for rare diseases to optimize outcomes with input from centers with expertise.

Introduction

Histiocytic disorders are rare hematologic diseases that present with diverse clinical manifestations, ranging from single-site indolent disease to multi-organ involvement with substantial morbidity and mortality. Over the past decade, several of these have been recognized as hematopoietic neoplasms by the World Health Organization and classified into various subtypes by the Histiocyte Society.1,2 The most recent histiocytic disorder to be categorized as a neoplasm was Erdheim–Chester disease in 2016 following
the discovery of clonal MAPK-ERK (RAS-RAF-MEK-ERK) pathway mutations in most cases. Due to their rarity and non-specific manifestations mimicking other conditions and potential to involve a wide variety of organs, histiocytic disorders can often be misdiagnosed, resulting in diagnostic and therapeutic delays for several years. Hence, a multidisciplinary approach with coordinated input from relevant subspecialties may help attain a timely diagnosis and improve patient outcomes. In this study, we report the tumor board experience from first-of-its-kind Histiocytosis Working Group (HWG).

Materials and Methods

The HWG was established in June 2017 as an attempt to formalize interaction between sub-specialists engaged in the care of patients with histiocytic disorders, as well as advance education and research efforts for histiocytic disorders. In August 2019, the HWG was expanded into a consortium to include the University of Alabama at Birmingham. The HWG is composed of physicians in disciplines that contribute to the diagnosis or management of histiocytic disorders: cardiology, dermatology, endocrinology, hematology, molecular biology/informatics, pathology, neurology, pulmonology, radiology, and rheumatology. The group established monthly meetings to discuss cases of suspected or confirmed histiocytic disorders in a multidisciplinary format. With the onset of COVID-19 pandemic, the meeting transitioned to online-only mode using video conferencing, with participation from both institutions. Each meeting included discussion of two cases over a 40-min period. All patients were presented prospectively as they were seen in the clinic, and had active clinical problems/questions that needed to be addressed. The HWG tumor board format included case presentation, review of histopathologic and radiology findings, summary of existing literature, and open discussion among the members with the intent of developing recommendations by consensus. Once a case was presented to the group, the first step was to discuss whether there was any uncertainty of the diagnosis. Here we report the findings from discussion of cases seen at our institution and presented at HWG over the first 2 years since its inception, June 2017 to June 2019. The HWG recommendations were divided into two categories based on the outcome of tumor board review (1) change in diagnosis (included cases that had a change from initial diagnosis or establishment of a diagnosis), (2) change in treatment (included cases that had a change in prior treatment plan or the formulation of a new treatment plan). The charts of patients were retrospectively reviewed for this report to assess best response to therapy, clinical or radiographic, based on criteria described previously.

Results

During the study period of 2-year included in this report, 40 cases with a suspected histiocytic disorder were reviewed at the HWG tumor board. The initial diagnostic indications for presentation at HWG tumor board were: Erdheim–Chester disease (ECD, n = 13); Langerhans cell histiocytosis (LCH, n = 13); Rosai–Dorfman disease (RDD, n = 7); histiocytic sarcoma (n = 1); Langerhans cell sarcoma (n = 1); unclassifiable histiocytosis (n = 1); immunoglobulin G4-related disease (IgG4-related disease, n = 1), xanthogranuloma (n = 1), fibrous histiocytoma (n = 1), and IgG lambda paraproteinemia (n = 1). Cases were presented to the HWG tumor board by nonhematologic specialties in 18 (45%) instances, most notably including two cases each by pulmonology, neurology, endocrinology, rheumatology, internal medicine, gastroenterology, and orthopedics, respectively. Average number of subspecialties involved in HWG case discussion was 5 (range, 2-9). Histiocytosis Working Group tumor board recommendations led to significant changes in 24 (60%) patients. These included change in diagnosis (n = 11, 27%) and change in treatment (n = 13, 33%). Most notable diagnostic changes were seen among three patients who were initially diagnosed or suspected to have ECD but later had diagnoses changed to IgG4-related disease, tenosynovial giant cell tumor, and osteopetrosis, respectively, after histopathologic review (Figure 1). One case each of ECD and LCH was modified to ECD/RDD and ECD/LCH mixed histiocytosis, respectively, after histopathologic review. Similarly, a patient receiving chemotherapy for LCH was relieved when the diagnosis was modified to dermatopathic lymphadenopathy related to a skin rash, which is a benign skin condition. Notably, no diagnostic changes occurred among consults for RDD, histiocytic sarcoma, and Langerhans cell sarcoma. Two cases were presented to the tumor board twice to discuss treatment options, one with ECD that progressed on hydroxyurea and tocilizumab and was started on cobimetinib eventually leading to disease stabilization, and one with RDD that progressed after receiving cladribine and was treated with cobimetinib leading to a complete response (Table 1). One case of asymptomatic histiocytic sarcoma had spontaneous disease regression so was observed without therapy. The median follow-up duration for the cohort was 2.1 years (range, 1.5-2.4 years). At last follow-up, the overall response rate among the cohort of 24 patients that had a change in diagnosis or treatment was 63% (n = 15), with five complete responses and 10 partial responses. Eight (33%) patients had stable disease, and the response was unknown for one patient.

Discussion

Our report highlights the feasibility and critical role of first-of-its-kind multidisciplinary tumor board in histiocytic disorders. Due to the potential for multi-organ involvement and the pitfalls in histopathologic diagnosis of histiocytic disorders, such a format of case discussion can be extremely helpful to patients. One of the most notable findings of our report was that 45% of the cases were brought to the group by physicians from specialties other than hematologist who suspected a histiocytic disorder based on clinical features or histopathologic/radiographic review. As our group members spanned the breadth of medical subspecialties and were aware of potential disease associations and features of histiocytic disorders, they were able to direct the clinicians toward HWG for discussion. This highlights how the establishment of such a group can lead to increased awareness and capturing of these diagnoses, which would not have otherwise made their way to a hematologist within the same duration of time from onset of symptoms.

In our cohort, the time to formulation of a treatment plan was likely much shorter with opinions from each expert
rendered at the tumor board compared with the time taken for individual office visits with various specialists. Often, the concern with histiocytosis is underdiagnosis of the various disease subtypes. However, in our cohort, the major impact was a change in diagnosis of several patients from ECD or LCH to unrelated disorders. Erdheim–Chester disease features can mimic other bone disorders. Arriving at a diagnosis requires close collaboration between radiologist, pathologist, and hematologist/oncologist. After tumor board discussion, one ECD diagnosis was changed to osteopoikilosis, which can appear similar to ECD on radiographic review but is a benign finding.7 The other ECD consult was subsequently diagnosed as tenosynovial giant cell tumor, which led to a referral to the appropriate specialist and change in treatment. Similarly, a patient who was receiving chemotherapy for a malignant condition (LCH) was relieved to find out that his diagnosis was dermatopathic lymphadenopathy secondary to a benign skin condition.6 Moreover, in some instances, re-review of the radiologic imaging findings in light of clinical features led to new findings of previously uncovered organ involvement such as central nervous system and connective tissue. Several cases were treated successfully with off-label therapies such as MEK-inhibitors based on existing literature and our collective experience. There is a need to examine the utility of such multidisciplinary specialized evaluation for approval of off-label therapies in other rare diseases as well. During the course of case discussions, each specialty learned from others and the cumulative experience of the group increased over time. As we gained experience, we were able to recognize patterns and apply what we learned to the subsequent patient. Eventually, our experience from the case discussions led to the creation of the first consensus guidelines for diagnosis of ECD, LCH, and RDD.4

Given the rarity of histiocytic disorders coupled with non-specific histopathologic findings, and diagnostic criteria that are clinico-pathologic, it is recommended by most guidelines to consider an evaluation at a center with expertise in these diseases.8 Even the most common histiocytic neoplasm, LCH, has an incidence of 1-2 cases per million/year in the USA,9 which equates to about 700 new diagnoses in a year. With approximately 13 000 practicing oncologists in the USA, this translates to almost one case every 20 years per oncologist for LCH, and likely much less for ECD or RDD.10,11 As these patients often have to travel long distances to such referral centers, having a multidisciplinary tumor board is also potentially cost-effective for the care of patients with histiocytic disorders. It also provides a model for comprehensive evaluation of patients with other unrelated rare disorders by centers with expertise using similar tumor boards. Such online tumor board format can also allow participation from multiple academic as well as community centers. Whether this approach can be expanded further to allow for remote consultations especially during the pandemic needs discussions among patient organizations, physicians, and policy makers.

Figure 1. Chart depicting the change in diagnosis before and after Histiocytosis Working Group presentation.
Table 1. Cases with a change in diagnosis or treatment after presentation at the Histiocytosis Working Group tumor board.

| Serial no. | Presenting subspecialty | Initial diagnosis | Final diagnosis | HWG recommendations | Outcomes of HWG recommendations | Subspecialties providing input (N) |
|------------|-------------------------|-------------------|-----------------|---------------------|---------------------------------|-----------------------------------|
| 1          | Pulm                    | ECD               | IgG4-related disease | Diagnosis, treat for IgG4 disease | CR                              | 6                                 |
| 2          | Rheum                   | IgG4 disease      | ECD              | Diagnosis, treat with vemurafenib | SD                              | 6                                 |
| 3          | Hem                     | Xanthogranuloma   | ECD              | Diagnosis, treat with dabrafenib | PR                              | 4                                 |
| 4          | Hem                     | LCH               | Dermatopathic lymphadenopathy | Diagnosis, stop vinblastine chemotherapy | CR                              | 4                                 |
| 5          | Ophto                   | ECD               | IgG4-related disease | Diagnosis, treat for IgG4 disease | PR                              | 6                                 |
| 6          | Gastro                  | Fibrous histiocytoma | ECD               | Diagnosis, reduced dose vemurafenib | PR                              | 3                                 |
| 7          | IM                      | lgG lambda paraproteinem     | ECD/LCH overlap | Diagnosis, treatment with vemurafenib | Complete clinical response and partial radiographic response | 4                                 |
| 8          | Gastro                  | Unclassifiable histiocytosis | ECD               | Diagnosis, treatment with cladribine | SD                              | 6                                 |
| 9          | Hem                     | ECD               | PVS              | Diagnosis, referral to sarcoma clinic | PR                              | 5                                 |
| 10         | Hem                     | ECD               | ECD/RDD overlap | Diagnosis, discontinue vemurafenib | SD, AEs from vem improved         | 7                                 |
| 11         | Ortho                   | ECD               | Osteopikilosis   | Diagnosis, observation          | SD                              | 3                                 |
| 12         | Hem                     | ECD               | ECD              | Hydroxyurea → tocilizumab → cobimetinib | SD                              | 9                                 |
| 13         | Hem                     | RDD               | RDD              | Cladribine                      | PR                              | 5                                 |
| 14         | Hem                     | LCH               | LCH              | Cladribine                      | Unknown                         | 5                                 |
| 15         | Urology                 | ECD               | ECD              | Hematology consult, cobimetinib | CR                              | 6                                 |
| 16         | Neuro                   | ECD               | ECD              | Restart dabrafenib for CNS disease | PR                              | 4                                 |
| 17         | Ortho                   | LCH               | LCH              | NGS, observation               | SD                              | 5                                 |
| 18         | Hem                     | RDD               | RDD              | Cladribine → Cobimetinib        | Complete clinical response and partial radiographic response | 6                                 |
| 19         | Hem                     | LCS               | LCS              | Trametinib → pembrolizumab + RT | PR                              | 4                                 |
| 20         | Hem                     | HS                | HS               | Observation due to spontaneous regression | PR                              | 4                                 |
| 21         | Hem                     | ECD               | ECD              | Repeat biopsy, hydrocortisone for adrenal insufficiency, cobimetinib | SD, not on therapy | 4                                 |
| 22         | Hem                     | LCH               | LCH              | No LCH treatment as symptoms unrelated to it | SD                              | 6                                 |
| 23         | Neuro                   | Neuro-histiocytosis | Neuro-histiocytosis | MRI of knees, cobimetinib           | PR                              | 5                                 |
| 24         | Med Onc                 | LCH               | LCH              | Atypical findings for LCH, quit smoking | PR                              | 6                                 |

Abbreviations: HWG, Histiocytosis Working Group; ECD, Erdheim–Chester disease; LCH, Langerhans cell histiocytosis; RDD, Rosai–Dorfman disease; HS, histiocytic sarcoma; LCH, Langerhans cell sarcoma; Pulm, pulmonology; Rheum, rheumatology; Ophto, ophthalmology; Hem, hematology; Gastro, gastroenterology; IM, internal medicine; Ortho, orthopedics; Neuro, neurology; Med Onc, medical oncology; NGS, next generation sequencing; RT, radiation therapy; CR, complete response; PR, partial response; SD, stable disease; AE, adverse effects.

Acknowledgments

This study was presented at the 2019 Histiocyte Society Meeting in Memphis, TN.

Funding

The study was supported in part by the University of Iowa/Mayo Clinic Lymphoma SPORE CA97274 and the Walter B. Frommeyer, Jr., Fellowship Award in Investigative Medicine, University of Alabama at Birmingham (G.G.).

Conflict of Interest

N. Nora Bennani: Kymera, Vivision, Kyowa Kirin, Daiichi Sankyo Inc, Verastem (SAB); Robert Vassallo: Pfizer, Bristol Myers Squibb, Sun Pharma (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.
Author Contributions
Conception/design: G.G. and R.S.G. Provision of study material or patients: G.G. and R.S.G. Collection and/or assembly of data: G.G., J.P.A., R.S.G. Data analysis and interpretation: G.G., J.P.A., R.S.G. Manuscript writing: G.G., J.P.A., R.S.G. Final approval of manuscript: All Authors.

Data Availability
The data underlying this article will be shared on reasonable request to the corresponding author.

References
1. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: International Agency for Research on Cancer, 2017.
2. Emile JF, Abla O, Fraitag S, et al.; Histiocyte Society. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016;127(22):2672-2681.
3. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov. 2016;6(2):154-165.
4. Goyal G, Young JR, Koster MJ, et al.; Mayo Clinic Histiocytosis Working Group. The mayo clinic histiocytosis working group consensus statement for the diagnosis and evaluation of adult patients with histiocytic neoplasms: erdheim-chester disease, langerhans cell histiocytosis, and rosai-dorfman disease. Mayo Clin Proc 2019;94(10):2054-2071.
5. Goyal G, Shah MV, Call TG, Litzow MR, Hogan WJ, Go RS. Clinical and radiologic responses to cladribine for the treatment of Erdheim-Chester disease. JAMA Oncol 2017;3(9):1253-1256.
6. Ravindran A, Goyal G, Failing JJ, Go RS, Rech KL. Florid dermatopathic lymphadenopathy- A morphological mimic of Langerhans cell histiocytosis. Clin Case Rep 2018;6(8):1637-1638.
7. Ihde LL, Forrester DM, Gottsegen CJ, et al. Sclerosing bone dysplasias: review and differentiation from other causes of osteosclerosis. Radiographics 2011;31(7):1865-1882.
8. Goyal G, Heaney ML, Collin M, et al. Erdheim-chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood 2020;135(22):1929-1945.
9. Goyal G, Shah MV, Hook CC, et al. Adult disseminated Langerhans cell histiocytosis: incidence, racial disparities and long-term outcomes. Br J Haematol 2018;182(4):579-581.
10. 2020 Snapshot: State of the oncology workforce in America. JCO Oncol Pract 2021;17:30.
11. Ravindran A, Gonsalves WI, Hashmi SK, et al. Estimating the annual volume of hematologic cancer cases per hematologist-oncologist in the United States: are we treating rare cancers too rarely? Leuk Lymphoma 2017;58(1):251-252.