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## Case Report

# ALK-positive histiocytosis involving the cavernous sinus: A deceptive radiologic mimic of meningioma<sup>☆,☆☆</sup>

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## ARTICLE INFO

## Article history:

Received 17 February 2023

Accepted 17 March 2023

## Keywords:

ALK-positive histiocytosis

Histiocytosis

Cavernous sinus

Magnetic resonance imaging

Meningioma

## ABSTRACT

Anaplastic lymphoma kinase (ALK)-positive histiocytosis is an uncommon condition, recently considered a separate condition from other histiocytosis by WHO 5th edition. It can involve intracranial structures. This manuscript describes a case of ALK-positive histiocytosis of the cavernous sinus, focusing on the radiologic and pathologic presentation of the entity. Our case had MRI manifestations mimicking meningioma, metastasis, and Langerhans histiocytosis. On CT imaging, benign osseous remodeling of the cavernous sinus was detected, which can be helpful in differentiating it from more common meningioma.

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<sup>☆</sup> Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

<sup>☆☆</sup> Competing Interests: The authors have declared that no competing interests exist.

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<https://doi.org/10.1016/j.radcr.2023.03.034>

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## Introduction

Anaplastic lymphoma kinase (ALK)-positive histiocytosis is an uncommon disorder that has been recognized as a distinct hematopoietic neoplasm by the WHO 5th edition [1]. It involves a variety of organs and tissues, including the liver, spleen, digestive tract, bone marrow, skin, breast, and central nervous system (CNS) [2]. Although both adolescents and adults may be diagnosed with ALK-positive histiocytosis, the former are more likely to have a disseminated illness affecting the liver, spleen, or bone marrow [3] predominantly. Adolescent patients usually present with hepatosplenomegaly, thrombocytopenia, and anemia. Invasion of the central nervous system by ALK-positive histiocytosis may cause headaches, nausea, and seizures, amongst other symptoms.

The cavernous sinus is a complex structure with the possibility of several vascular, neoplastic, and inflammatory etiologies. A portion of cavernous sinus lesions, nearly 15%, cannot be characterized entirely via the clinical, laboratory, and neuroradiologic workups. In this manuscript, we present a rare case of anaplastic lymphoma kinase (ALK)-positive histiocytosis of the cavernous sinus mimicking meningioma and discuss the neuroimaging manifestations.

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## Case study

A 30-year-old man with no significant past medical history initially presented for a 4-month history of diplopia. The initial MRI demonstrated a mass lesion centered at the right cavernous sinus encasing the cavernous segment of the internal carotid artery. The mass was isointense on T1 and FLAIR sequences and slightly low signal on T2 compared to the brain parenchyma and without diffusion restriction (Fig. 1, top row). The imaging findings were most suggestive of meningioma, and conservative treatment with a follow-up MRI was suggested. The patient's symptoms gradually worsened in the following months, and subsequent MRI without and with contrast 14 months later demonstrated interval enlargement of the mass with avid homogeneous enhancement (Fig. 1 middle row). After discussion in the tumor board, a biopsy via open right craniotomy was recommended for a definite diagnosis. Presurgical brain CT demonstrated an isodense mass in the right cavernous sinus with expansion and underlying osseous remodeling without osseous erosion (Fig. 1 bottom row). The gross surgical specimen exhibited tan-red tissue fragments. On microscopic evaluation (Fig. 2), the hematoxylin and eosin (H&E) stained sections showed a dense inflammatory infiltrate composed of small mature lymphocytes admixed with histiocytes and plasma cells. Histopathologic examination revealed no meningotheelial lesions. The evaluation revealed no morphologic or immunophenotypic features of peripheral nerve sheath tumor, primary malignant epithelioid neoplasm, or a lymphoid neoplasm. However, a subset of the CD68 and CD163-positive histiocytes demonstrated co-expression of cyclin D1, S100, and Factor XIIIa (variable), and these were uniformly negative for CD1a and BRAF V600E. Morphologi-

cally, the S100-positive histiocytes were characterized by enlarged round to oval nuclei with small distinct nucleoli variably clumped chromatin and abundant pale eosinophilic cytoplasm (Fig. 2 H&E, red arrow); these findings together raised the possibility of a histiocytic neoplasm, specifically Rosai-Dorfman disease. An OCT2 immunostain was subsequently performed which was negative in the lesional cells of interest, arguing against RDD [4]. Other histiocytic neoplasms including Langerhans cell histiocytosis were excluded by negative CD1a immunostain [5], and further the lack of systemic radiologic findings on PET-CT imaging studies other than hypermetabolic residual right cavernous lesion excluded Erdheim-Chester disease [6]. At this point, ALK (5A4 clone, Leica) was performed which showed positivity in the lesional histiocytes of interest. Given this finding, ALK-positive histiocytosis was considered, which was confirmed by the presence of KIF5B-ALK fusion by next-generation sequencing studies. Currently, the patient is being treated by Stereotactic Radiotherapy with the potential consideration of an ALK-inhibitor therapy in the future.

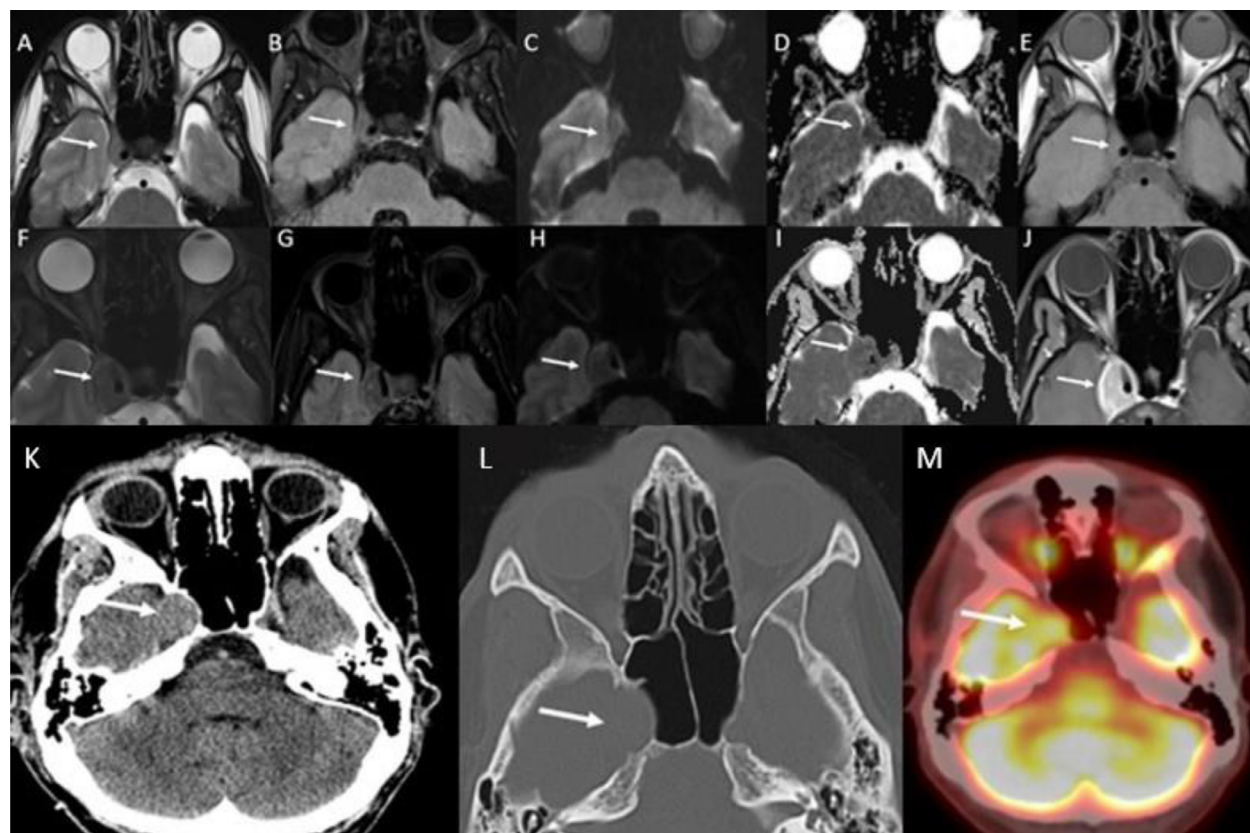
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## Discussion

Histiocytic disorders are scarce and often affect multiple organ systems; these lesions can pose diagnostic challenges. In 2008, Chan et al. disclosed for the first time three infants with a new form of systemic histiocytosis defined by ALK positivity in large CD163+ histiocytes with varying expression of other histiocyte/dendritic cell markers (S100, fascin, factor XI-Ia) [3]. Clinically, the condition was distinguished by the involvement of the liver and hematological system and might be mistaken for a storage problem or leukemia. The condition has the propensity to settle slowly, sometimes even without particular therapy but with supportive care. Recent findings have demonstrated ALK-positive histiocytosis in older children and adults with single- or multisystemic conditions, extending the first observation of the disease as a systemic condition of infants. In addition, the common existence of KIF5B-ALK fusions has been documented [7], and some patients have been successfully treated with ALK inhibition [2,8,9].

Based on Histiocyte Society, differential diagnosis of ALK-Histiocytosis from other types of histiocytosis, including Langerhans cell histiocytosis (LCH), Erdheim-Chester (ECD), juvenile xanthogranuloma (JXG), and Rosai-Dorfman disease (RDD) rely mainly on pathological and molecular identification of ALK translocation in combination with appropriate clinical and radiological findings [10]. Although previous studies of ALK-positive histiocytosis were case reports, 19 patients (49%) in the study by Kemps et al. [11] had CNS involvement. Observed neurological manifestations in this study include multiple solid brain tumors, leptomeningeal enhancement along the descending cauda equina nerve roots, insular tumor, left optic nerve tumor, large extramedullary intradural tumor at the C1-C2 level, large contrast-enhancing tumor in the peripontine cistern and compression of the pons. Isolated cavernous sinus involvement was not a reported finding.

The characteristic immunophenotype of LCH includes expression of CD1a, S100 protein, and langerin (CD207). But



**Fig. 1 – Initial MRI (top row) shows a mass lesion in the right cavernous sinus encasing the internal carotid artery, which is mildly hypointense to brain parenchyma on T2 sequence (arrow, A), iso-signal on FLAIR (arrow, B), without significant diffusion restriction (arrows, DWI; C and ADC map; D), and iso-signal on T1 sequence (arrow E). Follow-up MRI 14 months later (middle row), shows interval mass enlargement, which is mildly hypointense on T2 sequence (arrow, F), iso-signal on FLAIR (arrow, G), without diffusion restriction (arrows, DWI; H and ADC map; I), and with avid enhancement after contrast injection (arrow, J). No narrowing of the carotid artery was noted. Noncontrast CT with brain window shows an isodense mass at the right cavernous sinus (arrow, K). In addition, there is osseous remodeling around the cavernous sinus (arrow, L), with FDG uptake on PETCT (arrow, M).**

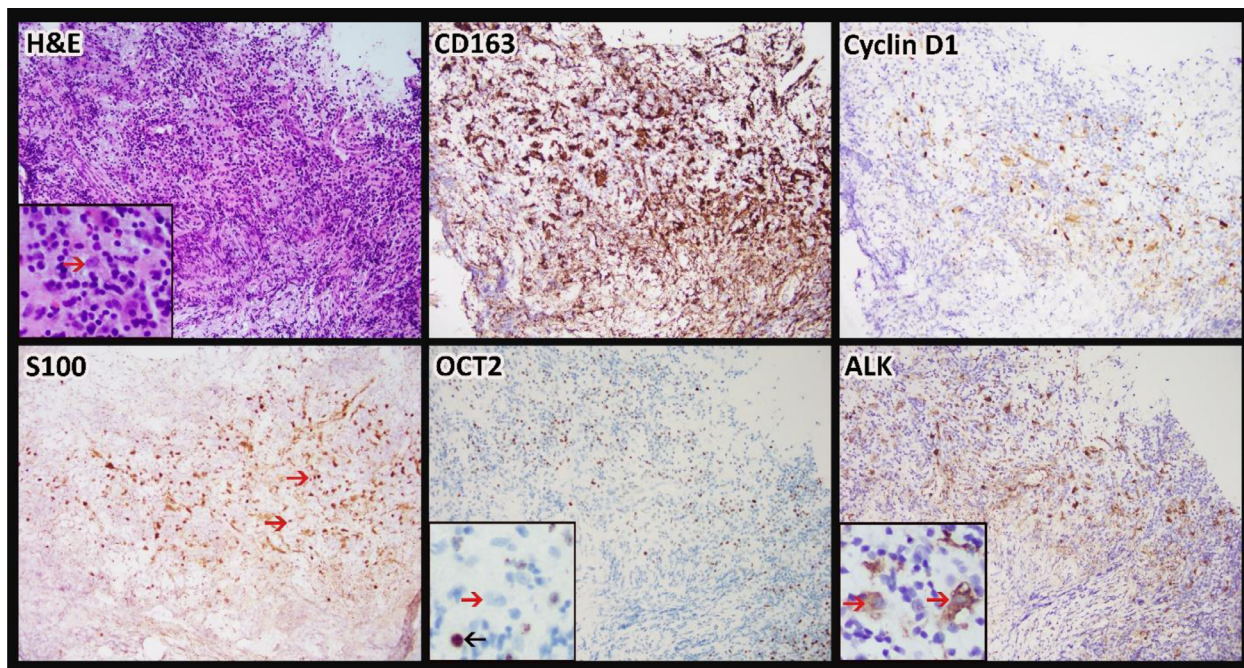
on the other hand, CD1a and langerin are both negative for JXG and RDD [12,13]. Based on histology, ECD presents loose clusters of classical foamy or granular histiocytes with well-defined cell borders and tissue infiltration by small CD1a and Touton cells [14]. Immunohistochemical stains are positive for CD68, CD163, CD14, factor XIIIa, BRAF VE1; and negative for CD1a, CD207 and S100. The PET-CT scan is recommended for all adults with suspected or histologically confirmed ECD. All patients should undergo chest, abdomen, and pelvis CT scans to detect pulmonary, vascular, and retroperitoneal invasion [10,15]. JXG consists of multiple reddish papules that develop into a yellow-brown color [10]. Foamy and Touton giant cells can be the differential diagnosis of juvenile xanthogranuloma and Erdheim-Chester disease [16]. The nuclei of juvenile xanthogranuloma are round to oval and are negative for S100 and CD1a [17]. A combination of CD11c, CD4, CD1a, and CD163 or CD68 staining provides a more specific diagnostic outcome to distinguish JXG from other histiocytic diseases [18]. In RDD, enlarged cervical lymph nodes are a classic finding. However, as with other types of histiocytosis, virtually any organ can be affected [10]. CNS involvement of RDD consists of a meningeal

mass that mimics a more diffuse pattern with dural thickening or meningitis [19].

Neuroimaging plays a crucial role in the diagnosis of cavernous sinus lesions. Lesions of the cavernous sinuses can often be suggested accurately by following the signal characteristics on different MRI sequences [20]:

1. T2 hyperintense lesion with complete FLAIR signal suppression: Probably an **arachnoid cyst**
2. T2 hyperintense with partial FLAIR signal suppression: Probably an **epidermoid cyst**
3. T2 hyperintense lesion without FLAIR signal suppression with T1 hyperintense intensity: Probably **dermoid or lipoma**
4. T2 hyperintense lesion without FLAIR suppression without T1 hyperintense intensity with homogeneous enhancement, internal carotid artery narrowing, and dural tail sign: Probably **meningioma**
5. T2 hyperintense lesion without FLAIR signal suppression, without T1 hyperintense intensity with homogeneous enhancement but without internal carotid artery narrowing or dural tail sign: Probably **hemangioma**





**Fig. 2 – Light microscopy of the cavernous sinus lesion biopsy shows involvement by an inflammatory infiltrate showing histiocytes characterized by enlarged round to oval nuclei with small nucleoli, and abundant pale eosinophilic cytoplasm (red arrows, H&E: Hematoxylin and eosin). These histiocytes are positive for CD163, cyclinD1, S100 (red arrows), and ALK (red arrows) and are uniformly negative for OCT2 (red arrow). Note that OCT2 stains background reactive small B-cells (black arrow, inset). Magnification: all images x200.**

6. T2 hyperintense lesion without FLAIR signal suppression, without T1 hyperintense intensity, without enhancement with bone destruction: Probably **metastasis**
7. T2 hyperintense lesion without FLAIR signal suppression, without T1 hyperintense intensity, without enhancement, without bone destruction: Probably **schwannoma**
8. T2 iso or hypointense lesion with plaque-like morphology with signal void structures: Probably **carotid-cavernous fistula**
9. T2 iso or hypointense lesion with plaque-like morphology without signal void structures: Probably **chronic inflammation or meningioma**
10. T2 iso or hypointense lesion with mass-like morphology, with T1 hyperintensity: Probably **melanoma**
11. T2 iso or hypointense lesion with mass-like morphology, without T1 hyperintensity without substantial diffusion restriction: Probably **meningioma** versus **metastasis** versus **Langerhans histiocytosis**
12. T2 iso or hypointense lesion with mass-like morphology, without T1 hyperintensity with significant diffusion restriction: Probably **lymphoma**

According to this approach, our case fits within number 11. Differentiation between meningioma and histiocytosis on imaging is very challenging, it's very well-known and they can present with similar imaging manifestations.

Our case also demonstrated expansion of the cavernous sinus with benign-looking osseous remodeling. Osseous remodeling can potentially differentiate (ALK)-positive histiocytosis from meningioma (given the fact that the classical manifesta-

tion of meningioma is hyperostosis), but this must be proven in the future. Also, our case demonstrated FDG uptake in the lesion equal to the brain parenchyma.

## Conclusion

ALK-positive histiocytosis is a rare and recently described condition with diagnosis mainly based on histology and molecular methods. It can involve the intracranial structures (cavernous sinus in this case). In our case, it presented with mild T2 hypointensity, T1, and FLAIR isointensity, with avid enhancement without diffusion restriction, mimicking meningioma, metastasis, and Langerhans histiocytosis. Benign osseous remodeling can potentially differentiate this condition, but this sign must be evaluated in the future.

## Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

## Patient consent

Informed consent was obtained from the patient upon admission. According to our university's ethical guidelines, no addi-

tional IRB approval is needed for case report publication with fewer than 3 patients.

### Availability of supporting data

N/A

### Author contributions

H.S., A.S., M.A.: Conception and design of work; A.R., R.C., and G.G.: Histopathologic diagnosis; M.H., A.SH., R.SH.: Data collection; H.S., A.S., R.Ch., G.G., A.R.: Data analysis, and interpretation; M.A., R.SH., M.KH., A.S., H.S.: Manuscript writing; M.A., M.KH., R.Ch., G.G., A.R.: Critical revision of the article; M.A., H.S., A.S., R.Ch., G.G., A.R.: Final approval of the version to be published; H.S., A.S., M.A.: Supervision; A.R., R.Ch., G.G., M.H., M.KH.: Visualization.

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

### REFERENCES

- [1] Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia* 2022;36:1703–19.
- [2] Qiu L, Weitzman SP, Nastoupil LJ, Williams MD, Medeiros LJ, Vega F. Disseminated ALK-positive histiocytosis with KIF5B-ALK fusion in an adult. *Leuk Lymphoma* 2021;62:1234–8.
- [3] Chan JK, Lamant L, Algar E, Delsol G, Tsang WY, Lee KC, et al. ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. *Blood* 2008;112:2965–8.
- [4] Ravindran A, Goyal G, Go RS, Rech KL. Mayo clinic histiocytosis working group Rosai-Dorfman disease displays a unique monocyte-macrophage phenotype characterized by expression of OCT2. *Am J Surg Pathol* 2021;45:35–44.
- [5] Goyal G, Tazi A, Go RS, Rech KL, Picarsic JL, Vassallo R, et al. International expert consensus recommendations for the diagnosis and treatment of Langerhans cell histiocytosis in adults. *Blood* 2022;139:2601–21.
- [6] Goyal G, Heaney ML, Collin M, Cohen-Aubart F, Vaglio A, Durham BH, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. *Blood* 2020;135:1929–45.
- [7] Chang KTE, Tay AZE, Kuick CH, Chen H, Algar E, Taubenheim N, et al. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. *Mod Pathol* 2019;32:598–608.
- [8] Kashima J, Yoshida M, Jimbo K, Izutsu K, Ushiku T, Yonemori K, et al. ALK-positive histiocytosis of the breast: a clinicopathologic study highlighting spindle cell histology. *Am J Surg Pathol* 2021;45:347–55.
- [9] Sugiyama M, Hirabayashi S, Ishi Y, Kikuchi J, Ishikura A, Motegi H, et al. Notable therapeutic response in a patient with systemic juvenile xanthogranuloma with KIF5B-ALK fusion. *Pediatr Blood Cancer* 2021;68:e29227.
- [10] Emile J-F, Cohen-Aubart F, Collin M, Fraitag S, Idbaih A, Abdel-Wahab O, et al. Histiocytosis. *Lancet* 2021;398:157–70.
- [11] Kemps PG, Picarsic J, Durham BH, Fraitag S, Idbaih A, Abdel-Wahab O, et al. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition. *Blood* 2022;139:256–80.
- [12] Harmon CM, Brown N. Langerhans cell histiocytosis: a clinicopathologic review and molecular pathogenetic update. *Arch Pathol Labor Med* 2015;139:1211–14.
- [13] Haupt R, Minkov M, Astigarraga I, Schäfer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer* 2013;60:175.
- [14] Ozkaya N, Rosenblum MK, Durham BH, Pichardo JD, Abdel-Wahab O, Hameed MR, et al. The histopathology of Erdheim-Chester disease: a comprehensive review of a molecularly characterized cohort. *Mod Pathol* 2018;31:581–97.
- [15] Haroche J, Arnaud L, Cohen-Aubart F, Hervier B, Charlotte F, Emile JF, et al. Erdheim-Chester disease. *Rheumat Dis Clin* 2013;39:299–311.
- [16] Lucas C-HG, Gilani A, Solomon DA, Liang X, Maher OM, Chamyam G, et al. ALK-positive histiocytosis with KIF5B-ALK fusion in the central nervous system. *Acta Neuropathol* 2019;138:335–7.
- [17] Palomino Portilla EA, Ayquipa Arróspide TD, Torpoco Baquerizo IG, Huallanca MAM, Quiñones Ávila MDP. Juvenile xanthogranuloma: clinical-pathological approach. *Case reports. Revista de la Facultad de Medicina Humana* 2021;22:19.
- [18] Salari B, Dehner LP. Juvenile and adult xanthogranuloma: A 30-year single-center experience and review of the disorder and its relationship to other histiocytoses. *Ann Diagn Pathol* 2022;58:151940.
- [19] Andriko J-AW, Morrison A, Colegial C, Davis BJ, Jones RV. Rosai-Dorfman disease isolated to the central nervous system: a report of 11 cases. *Mod Pathol* 2001;14:172–8.
- [20] Mahalingam HV, Mani SE, Patel B, Prabhu K, Alexander M, Fatterpekar GM, et al. Imaging spectrum of cavernous sinus lesions with histopathologic correlation. *Radiographics* 2019;39:795–819.