GR GR GR

^{Q6} Kevin Michael Cachapero Moalong¹, Jose Danilo Bengzon Diestro⁷, Adrian Isidoro Espiritu^{1,6}, Josephine Anne Cuevas Lucero^{2,3}, Aeron Patrick Roy L. de la Cruz², Jeffrey Matubis Valencia^{2,4}, Enrique Melarin Chua III⁵, Alvin Rae Francisco Cenina¹, Julian Spears^{7,8}, Ma Cristina. Zarsadias San Jose¹

Key words

- Carotid artery aneurysm
- Endovascular
- Hypereosinophilic syndrome
- Stroke

Abbreviations and Acronyms

CT: Computed tomography HES: Hypereosinophilic syndrome

PDGFRA: Platelet-derived growth factor receptor alpha

From the ¹Department of Neurosciences, Division of Adult Neurology, ²Department of Medicine, ³Division of Hematology, ⁴Division of Cardiology, ⁵Department of Surgery, Division of Thoracic and Cardiovascular Surgery, and ⁶Department of Clinical Epidemiology, University of the Philippines—College of Medicine, University of the Philippines, Manila, Philippines; and ⁷Department of Medical Imaging, Division of Diagnostic and Therapeutic Neuroradiology, St. Michael's Hospital, University of Toronto and ⁸Department of Surgery, Division of Neurosurgery,

0.3 University of Toronto, Toronto, Canada

To whom correspondence should be addressed: Kevin Michael Cachapero Moalong, M.D. [E-mail: kevin.moalong@gmail.com]

Citation: World Neurosurg. (2020). https://doi.org/10.1016/j.wneu.2020.04.119

Journal homepage: www.journals.elsevier.com/worldneurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter \odot 2020 Elsevier Inc. All rights reserved.

INTRODUCTION

Hypereosinophilic syndrome (HES) is a rare condition with protean manifestations classically defined by elevated eosinophil counts greater than 1500/mm³ for more than 6 months that is associated with presumptive end-organ involvement in the absence of evidence for typical causes of eosinophilia such as parasitism or allergies.¹ The central nervous system has been implicated as a potential site of organ damage, presenting with ischemic stroke.² Vascular abnormalities such as aneurysms also have been documented to complicate HES.³ To date, however, no cases of HES associated with carotid OBJECTIVE: To describe a case of an adult female Filipino with hypereosinophilia and bilateral carotid artery aneurysms who subsequently developed bilateral cerebral hemisphere strokes following aneurysm stenting.

• CASE DESCRIPTION: A 57-year-old female patient with persistent hypereosinophilia presented with progressively enlarging bilateral neck masses, revealed to be carotid artery aneurysms on computed tomography angiography. Following surgical exploration, she later developed right-sided hemiplegia, aphasia, and right hemianopia. Cranial computed tomography revealed infarcts on both middle cerebral artery territories. Bone marrow biopsy and fluorescent in situ hybridization revealed findings suggestive of hypereosinophilic syndrome. She was started on standard aspirin and statin therapy and was discharged sixteen days after the procedure. Partial improvement of neurologic deficits was noted two months later on follow up. Chemotherapy with imatinib was initiated.

CONCLUSIONS: This patient's prothrombotic state from FIP1L1-PDGFRA positive hypereosinophilia may have led to large carotid artery aneurysm formation and intramural thrombosis. This case demonstrates a possible and heretofore undocumented neurovascular sequela of hypereosinophilic syndrome.

aneurysms have been reported. Treatment of such aneurysms includes endovascular stent placement, which carries a 30-day stroke risk of 5.16%.⁴ Bilateral hemisphere strokes following stenting are rare complications and have not as of yet been documented in literature.

In this report, we describe a case of an adult Filipino female with hypereosinophilia and bilateral carotid artery aneurysms who subsequently developed bilateral cerebral hemisphere strokes following aneurysm stenting.

CASE DESCRIPTION

A 57-year-old right-handed non-atopic adult female Filipino initially presented at the outpatient clinics with a 1-year history of gradually enlarging bilateral pulsatile neck masses, larger on the left with associated generalized pruritus (Figure 1A-B). The progressive enlargement of these masses prompted her to seek a consultation at a tertiary hospital, upon which imaging and possible biopsy of the masses were planned. At the time, no neurologic deficits were noted. She also had hypertension controlled by medications. Her family medical and personal social history were both unremarkable. 59 60

61

62 63

64

65

66 67

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

00

91

92

93

94

95

96

97

98

99

100

101

102

103

104

105

106

107

108

100

110

III

112

113

114

115

116

Computed tomography (CT) angiography of the neck showed 3 sacculofusiform tortuous aneurysms arising from the cervical segments of both internal carotid arteries (2 on the left). The largest aneurysm at the carotid bifurcation on the left side measured 47 mm in the greatest dimension. A mural thrombus measuring 16 mm was visualized within this aneurysm (Figure 1C). A catheter angiogram further delineated the anatomy of the aneurysms (Figure1D–E). Screening for other aneurysms with cranial, chest, and

ARTICLE IN PRESS



Figure 1. Among the 3 identified carotid artery aneurysms, the proximal left carotid artery aneurysm is the largest one. (**A**) Lateral view. (**B**) Anteroposterior view demonstrating the prominent neck mass created by the left internal carotid artery aneurysm. (**C**) Computed tomography scan of the carotids on axial view demonstrates the large unfilled portion of the aneurysm representing a large mural thrombus (*white arrow*) (**D**) Catheter angiography lateral view of the right carotid artery aneurysm measuring 21 mm \times 34 mm \times 18 mm involving the distal common carotid and proximal regions of both external and internal carotid arteries. (**E**) Anteroposterior view of the left internal carotid artery aneurysms. The more proximal larger aneurysm (*white arrow*) measures 51 mm \times 4.1 mm \times 30 mm and internal carotid arteries whereas the smaller distal aneurysm (*arrowhead*) measures

12 mm × 21 mm × 9.1 mm and involves the mid-cervical segment of the left internal carotid artery. (F) The final run showing well-apposed stents and demonstrating absence of filling of the proximal left internal carotid artery aneurysm. (G) Hypodensities on both middle cerebral artery territories are seen at the left frontoparietal area (*white arrow*) and the right frontal area (*arrowhead*). (H) Bone marrow core shows a hypercellular marrow for age, with 80%–90% cellularity (160× magnification, hematoxylin and eosin [H&E]) Bar = 200 µm. (I) Bone marrow aspirate smears show erythrogranulopoiesis with maturation and presence of clusters of eosinophils (*) (160× magnification, H&E) bar = 200 µm. (J) The marrow is cellular and polymorphous with clusters of eosinophils (*) seen comprising 15%–20% of the total cell population (400× magnification).

abdominal CT angiography were negative. Persistently elevated eosinophil levels as high as 13,500/mm³ were found with repeat testing (**Table 1**). Stool examination for intestinal parasitism and workup for autoimmune processes viz. antinuclear antibody and antineutrophil cytoplasmic antibody all yielded negative results. Because of the high risk of ischemic stroke associated with large thrombus-filled carotid artery aneurysm, a stenting procedure was planned for the largest aneurysm.

The patient underwent surgical exploration of the left neck to isolate and ligate and the external carotid arteries to prevent an endovascular leak from this vessel after stent deployment. Unfortunately, the external carotid artery could not be isolated. After a difficult navigation through the patient's aortic arch with an 8-French Berenstein diagnostic catheter, 2 overlapping covered stents (6 mm \times 59 mm Atrium Advanta V12; Getinge, Gothenburg, Sweden) were sequentially deployed at 8 atm (6 mm) across the neck of the larger aneurysm on the left. An angiogram done confirmed adequate placement of the stents and excluded any endovascular leaks. An open procedure with the goal of decreasing the aneurysm size with thrombus removal and aneurysm wall biopsy was attempted. However,

Table 1. Serial Complete Blood Counts Showing Persistently Elevated Eosinophils								
Cells	Unit	May 15	Sep 6	Sep 23	Oct 15	Oct 23	Oct 25	Oct 27
WBC	10 ⁹ /L	14.30	19.9	19.50	17.80	13.8	13.7	14.4
Eos		0.55	0.68	0.64	0.55	0.24	0.32	0.34
AEC	10 ⁹ /L	7.87	13.5	12.48	9.79	3.312	4.384	4.896
AEC	cells/mm ³	7870	13500	12480	9790	3312	4384	4896
WBC, white blood cells; Eos, eosinophils; AEC, absolute eosinophil count.								

print & web 4C/FPC

ARTICLE IN PRESS

during this maneuver, the installed stents were inadvertently displaced, resulting in recurrent filling of the aneurysm in a subsequent angiogram. A balloon was brought up into the stent and inflated to improve apposition to the vessel wall. A repeat angiogram confirmed the absence of an endovascular leak (Figure 1F). The plan for thrombus removal and vessel wall biopsy was aborted.

233

234

235

236

237

238

239

240

241

242

243

244

245

246

247

248

249

250

251

252

253

254

255

256

257

258

259

260

261

262

263

264

265

266

267

268

269

270

271

272

273

274

275

276

277

278

279

280

281

282

283

284

285

286

287

288

289

200

Thirty-five minutes after the procedure, after emerging from anesthesia, the patient presented with aphasia, right homonymous hemianopia, and right hemiplegia. An urgent noncontrast cranial CT scan done ruled out a hemorrhage. Thrombolysis was not considered because of the surgical exploration that was done on the aneurysm. Because of the lack of endovascular thrombectomy capability in our institution, a cranial CT angiography was no longer pursued. A follow-up cranial CT scan done the next day revealed infarcts on both middle cerebral artery territories, the involvement of the left being more extensive than the right Q4 (Figure 2D). Subsequent stroke workups with transthoracic echocardiography and transcranial Doppler ultrasound revealed unremarkable findings. She was started on aspirin and statin therapy.

Persistent leukocytosis and eosinophilia on complete blood count prompted referral to the Hematology service. Hypereosinophilic syndrome was considered due to the presence of organ involvement. Bone marrow aspiration biopsy revealed a hypercellular marrow for age with clusters and sheets of eosinophilia seen with eosinophils comprising 15%-20% of the total cell population (Figure 1H–J). Fluorescence in situ hybridization identified CHIC2 gene deletion found on the FIP1L1 gene at chromosome 4q12. Sixteen days after her procedure, the patient was discharged with a modified Rankin Scale score of 4. She was last seen 2 months after discharge with partial improvement of her language and motor deficits but still had a modified Rankin Scale score of 4. Imatinib 400 mg was initiated in the clinic and a decrease in severity of pruritus was observed (Table 1). Unfortunately, the patient was eventually lost to follow-up despite the team's best efforts to locate her.

DISCUSSION

The case describes a patient who fulfills both the classic criteria for HES and the proposed new definition, which accepts a shorter (1 month < 6 months) interval between repeat eosinophil count testing.^{1,5} The diagnosis is further bolstered by prominent eosinophilia on bone marrow biopsy and the presence of the CHIC2 deletion on fluorescence in situ hybridization. The presence of CHIC2 deletion at 4q12 results in the formation of a tyrosine kinase fusion protein between FIP1L1 and platelet-derived growth factor receptor alpha (PDGFRA).⁶ Identification of the fusion protein confirms the diagnosis of a molecularly defined primary eosinophilia or myeloproliferative neoplasm with eosinophilia associated with FIP1L1-PDGFRA.7 Her only other risk factor for the development of carotid artery aneurysms was hypertension. We believe that given the number and size of her aneurysms and the clonal cause for hypereosinophilia, the vascular pathology is unlikely to be from hypertension alone.

Before the discovery of imatinib, a review of 57 cases of HES reported a median survival of 9 months with a 3-year survival of 12%.⁶ The FIP1L1-PDGFRA fusion protein is the therapeutic target of imatinib, a multikinase inhibitor of PDGFRA, PDGFRB, KIT, and ABL.⁸ Imatinib rapidly induces deep molecular response in FIP1L1-PDGFRA—positive patients across multiple cohort studies at a dose of 100—400 mg. In the Mayo cohort, the median survival has not been reached and clinical outcomes remain excellent.⁷

A striking feature of this case was the development of large carotid artery aneurysms with mural thrombus formation. In HES, aneurysm formation can occur from intimal eosinophilic infiltration leading to tissue damage and vascular wall destruction—these aneurysms have been reported to arise in the coronary, mesenteric, and peripheral arteries.⁹ The carotid arteries, however, have not been implicated in HES per the existent literature. HES also has been associated with an increased propensity for thrombosis that could have contributed to the formation of our patient's 16-mm mural thrombus.¹⁰

A review on the treatment of extracranial carotid artery aneurysms found an

advantage to treating these aneurysms in terms of stroke and mortality. Indications for surgery include large aneurysm size, mural thrombus, aneurysm growth, thromboembolic events, and rupture.4,11 Given the aneurysm size (51 mm) and presence of a 16 mm mural thrombus in our patient, we felt that a stenting procedure was warranted for primary stroke prevention. The occurrence of contralateral ischemic stroke immediately following carotid artery stent placement is rare but has been reported.12 We believe this complication in our case is likely from aneurysm thrombus disruption and subsequent embolization. An extracranial-intracranial bypass with ligation/trapping also could have been an option.¹¹ The bypass would enable us to maintain flow in the artery whereas ligation would have prevented the thrombus particles from embolizing distally. Alternatively, if the patient passes a balloon test occlusion procedure, an outright ligation or balloon occlusion of the internal carotid artery also can be considered. A flow diverter may also be used for the smaller more distal part of the aneurysm if it shows changes in size and morphology in future imaging studies.

CONCLUSIONS

In summary, the case details a possible neurovascular sequela of HES (FIP1LI-PDGFRA—positive hypereosinophilia) heretofore undocumented in the existent literature: large carotid artery aneurysms.

REFERENCES

- Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. J Allergy Clin Immunol. 2010;126:45-49.
- Sethi HS, Schmidley JW. Cerebral infarcts in the setting of eosinophilia three cases and a discussion. Arch Neurol. 2016;67:1275-1277.
- Puri R, Dundon BK, Leong DP, Khurana S, Worthley MI. Hypereosinophilic syndrome associated with multiple coronary aneurysms. Int J Cardiol. 2009;133:e43-e45.
- Welleweerd JC, den Ruijter HM, Nelissen BGL, et al. Management of extracranial carotid artery aneurysm. Eur J Vasc Endovasc Surg. 2015;50:141-147. Q5
- 5. Valent P, Klion AD, Horny H-P, et al. Contemporary consensus proposal on criteria and

348

201

CL

KEVIN MICHAEL CACHAPERO MOALONG ET AL.

classification of eosinophilic disorders and related

- 9. McVeigh T, Hynes N, Tawfick W, Sultan S. Endovascular aneurysm repair for multiple aneurysms as a sequel of hypereosinophilic syndrome. Vasc Endovascular Surg. 2014;48:277-280.
- hypereosinophilic syndrome presenting with multiorgan thromboses associated with intestinal obstruction. Turkish J Hematol. 2013;30:311-314.
- artery aneurysms: Texas Heart Institute experience. J Vasc Surg. 2000;31:702-712.
- 12. Park S-H, Lee CY. Contralateral cerebral infarction after stent placement in carotid artery: an

2008;44:159-162.

POSSIBLE NEUROVASCULAR SEQUELA OF HES

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 18 January 2020; accepted 15 April 2020 Citation: World Neurosurg. (2020).

https://doi.org/10.1016/j.wneu.2020.04.119

Journal homepage: www.journals.elsevier.com/worldneurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2020 Elsevier Inc. All riahts reserved.

CASE REPORT

349

syndromes. J Allergy Clin Immunol. 2012;130: 607-612.eg. 6. Pardanani A, Ketterling RP, Brockman SR, et al.

- CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood. 2003;102: 3093-3096.
- 7. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. Am J Hematol. 2017;92:1243-1259.
- 8. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in

- 10. Sui T, Li Q, Geng L, Xu X, Li Y. A case of
- 11. El-Sabrout R, Cooley DA. Extracranial carotid

unexpected complication. J Korean Neurosurg Soc.

368

369