Granulomatosis with Polyangiitis: Brain and Head and Neck Findings

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Learning objectives

1. To review the brain and head & neck imaging manifestations of Granulomatosis with Polyangiitis (GPA).

2. To describe the role of CT and MRI in its diagnosis and the key imaging findings.

3. To review the differential diagnosis.
Background

GPA, formerly known as Wegener's granulomatosis, is a necrotizing granulomatous vasculitis of small and medium-sized vessels that affects lungs, the upper respiratory tract and kidneys but any organ may be involved including the CNS. It is a rare disease, more frequent in caucasian males with a prevalence of 3:100,000 in the USA and a prevalence in European countries ranging from 24 to 157 cases per million.

Two of the following 4 criteria are required to make the diagnosis based on the 1990 American College of Rheumatology criteria and/or the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides: (1) nasal or oral inflammation, (2) respiratory radiographic abnormalities (nodules, infiltrates, and cavities), (3) microhematuria or red blood cell casts on urinary sediment analysis, and (4) granulomatous inflammation demonstrated by biopsy.

There are 2 clinical forms of GPA: those presenting with severe or with limited complications as a result of involvement of a vital organ(s).

Patients with limited GPA respond favorably to less toxic regimens of methotrexate and glucocorticoids, whereas those with severe GPA often require aggressive therapy with glucocorticoids in addition to cyclophosphamide.

Although the final diagnosis requires biopsy, the presence of vasculitis, necrosis, and granulomatous inflammation is seen in only 16% of nasal biopsies. GPA is associated with positive anti-neutrophil cytoplasmic antibody (ANCA) however this may be undetectable.

Among patients with GPA, approximately 90% have nasal, sinus, or ear involvement. Even though GPA affects the CNS less frequently (7%-11), its involvement has led to recent clinical attention because of its high association with refractory disease.
Findings and procedure details

Here we review imaging findings in 15 patients with GPA seen at our institution between 1995-2014. Findings were classified according to location and imaging features.

HEAD AND NECK FINDINGS:

Nasosinusal Involvement

GPA causes a chronic rhinosinusitis with mucosal ulceration and granuloma formation within the nasal cavities that may lead to osseous erosion, progressive destruction of cartilage and neo-osteogenesis but sparing of the hard palate.

A nasal granuloma is seen as a soft-tissue mass at CT and is hypointense on T2- and T1-weighted MR sequences, with variable degrees of contrast enhancement. In the chronic phase, the walls of the residual paranasal sinuses demonstrate marked thickening, whereas the sinus volume is gradually reduced and the residual lumen may be filled with material having a "ground-glass" appearance. (Figure 1). Erosion of the nasal septum is very common, resulting in a large single sinus cavity. Destruction of the hard palate with sinonasal-oral fistulas may also be seen. Presence of chronic rhinosinusitis associated with positive ANCA with specific antibodies to proteinase 3 (PR3) or myeloperoxidase (MPO) highly suggests GPA.

Differential diagnosis includes chronic sinusitis and other causes of nasal perforation, such a cocaine-induced necrosis, lymphoma (large midline soft-tissue mass with extensive tissue ulceration and a diffuse and permeative lymphomatous infiltrate with atypical lymphoid cells), sarcoidosis (noncaseating granulomas on biopsy), topical descongestants, microscopic polyangiits (associated with nasal polyps without necrotizing granulomatous inflammation, digital trauma (nose picking), immunoglobulin G4 (IgG4)-related disease (midline destructive lesion with nasal septal and palatal perforation, absent granulomas on biopsy, IgG4-positive plasma cells on immunohistochemical staining). (Figure 2).

Airway Involvement

It is a late complication seen in 55% of GPA patients. Circumferential mucosal thickening that progresses to subglottic stenosis, and presence of associated pulmonary cavitated nodules, strongly favors GPA. (Figure 3).
Amyloidosis can have similar features to those of GPA, but it is associated to submucosal airway and adenopathy. A tracheal neoplasm will show an eccentric mass, rather than circumferential thickening. Postintubation tracheal stenosis will follow a history of intubation. A subglottic granuloma is also a late-phase complication of intubation. Relapsing polychondritis characteristically spares the posterior membranous tracheal wall and usually associate auricular and nasal polychondritis. (Figure 4).

**Orbital Involvement**

Ophthalmologic manifestations have been reported in 40-50% of GPA patients in the form of orbital pseudotumor or small-vessel vasculitis. Orbital pseudotumor is a diffuse inflammatory infiltrate involving the intra or extraconal space with or without a contiguous sinonasal disease, causing proptosis and/or optic nerve compression with subsequent atrophy and visual loss. It can spread to the cavernous sinuses causing a Tolosa-Hunt syndrome. Small-vessel vasculitis can cause conjunctivitis, scleritis, episcleritis, uveitis, optic neuritis, optic nerve vasculitis, retinitis, central retinal artery ischemia, or cranial nerve paresis. On MRI T1- and T2-weighted images, orbital pseudotumor has low-to-intermediate signal. A low T2 signal is characteristic of GPA in the later stage of granulomatous transformation, but similar findings can be seen with idiopathic orbital inflammation, chronic lacrimal gland sarcoidosis and in metastatic melanoma of the orbit. After gadolinium injection, orbital pseudotumor granulomas may show homogenous or heterogeneous enhancement. (Figure 5).

Orbital sarcoidosis can show an enhancing intraorbital pseudotumor-like pattern and involve the lacrimal glands as can leukemia/lymphoma. Intraorbital postseptal cellulitis presents a subperiosteal abscess in the medial orbit wall and associated symptoms are fever and orbital swelling. Orbital inflammatory pseudotumour is an idiopathic inflammatory condition that most commonly involves the extraocular muscles including their tendinous insertions which distinguishes it from thyroid orbitopathy, where the insertions are spared. (Figure 6).

**Skull Base Involvement**

Is a result from direct extension from sinonasal or orbital disease. GPA can lead to neuropathy and the most frequently involved cranial nerves are the olfactory and optic nerves. MRI may reveal inflammatory changes with associated thickening and contrast enhancement of the adjacent cranial nerves.

**Temporal Bone Involvement**

Up to 40% of patients with GPA will otologic manifestations. Bilateral serous otitis media is the main finding and is caused by obstruction of the eustachian tubes resulting from
direct extension of adjacent sinonasal disease. Granulomatous inflammation can cause bone destruction. (Figure 7). The differential diagnosis includes coalescent otomastoiditis and osteoradionecrosis, but those entities are unilateral and osteoradionecrosis presents in the setting of head and neck cancer after radiation.

**Intracranial Involvement**

There are 3 different forms of GPA-related CNS disease. First, granulomatous tissue may spread from the nasal or paranasal cavities and invade the adjacent structures (orbit, optic nerve, chiasm, cranial nerves, brain, meninges, and/or pituitary gland). (Figure 8).

Second, is due to remote granulomatous intracerebral lesions of the brain, meninges, cranial nerves, or parietal bone.

The 3rd and most common parenchymal manifestation is cerebral small-vessel vasculitis that occurs in 4% of patients and affects a typical vascular distribution. MRI findings vary from unspecific multiple and bilateral high T2 signal intensity white matter lesions to infarcts. (Figures 9,10,11).

Differential diagnosis is progressive multifocal leukoencephalopathy (PML) particularly in patients GPA undergoing immunosuppressive therapy. PML characteristically involves subcortical U-fibers. ADEM is also a consideration but generally there is a history of recent vaccination or upper respiratory infection.

GPA pituitary involvement typically affects the posterior lobe. Findings include enlargement of the gland with loss of posterior high signal on T1-weighed images, thickening of the infundibulum and infiltrative lesions or enhancing lesions of the gland. (Figure 12). There are no specific imaging features of GPA pituitary involvement. Differential diagnosis of masses affecting the pituitary stalk is broad and includes: pituitary adenoma, Rathke cleft cyst, craniopharyngioma, chordoma, glioma, lymphoma, leukemia, metastasis and germinoma. (Figure 13). Several other types of inflammatory and infectious conditions may be part of the differential diagnosis and include sarcoidosis, tuberculosis, fungal infection, abscess, Langerhans cell granulomatosis, Tolosa-Hunt syndrome, IgG4-related hypophysitis, Ipilimumab hypophysitis.

Pachymeningitis is the most common form of GPA-related meningeal disease. (Fig. 14). Two distinct patterns of meningeal disease have been recognized. A focal form represents a direct spread of inflammation from contiguous sinonasal or orbital disease. The diffuse form has no relation to contiguous disease and shows a symmetric thickening and enhancement of the dura. The main symptom is severe headache refractory to treatment. Differential diagnosis are lymphoma, neurosarcoïd, and infectious meningitis. Both lymphoma and neurosarcoïdosis can present with dural masses, which is not a
typical feature of GPA. Neurosarcoid has an affinity for involving the pia rather than the dura and may show leptomeningeal enhancement. Infectious meningitis has a clinical history of fever and is a clinical diagnosis. (Figure 15).
**Fig. 1:** GPA Sinonasal Involvement in three different patients. Axial (upper row) and coronal (lower row) with bone window. a) Destructive sinusitis with erosion of the nasal septum and adjacent cartilage structures. b,c) Bilateral complete opacification of the maxillary, complete destruction of the central sinonasal bone and cartilage structures as well as septum resulting in a large single sinus cavity (*).  

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**Fig. 2:** Differential diagnosis of GPA nasal septum perforations and erosions (*).

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Fig. 3: GPA airway involvement in 3 different patients. a) Axial enhanced cervical CT shows circumferential mucosal thickening (*) partially obstructing the tracheal lumen. b,c) A different patient with GPA. Axial CT shows a concentric circumferential thickening of the mucosa causing partial subglottic stenosis (arrow in c). d,e) Axial MRI T1 weighted image of another patient shows a concentric circumferential thickening of the mucosa (*) partially obstructing the tracheal lumen. Note the bony maxillary sinus destruction in e).

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Fig. 4: Differential diagnosis of tracheal stenosis on axial contrast-enhanced CT. a,b) Tracheal neoplasms. a) Hemangioma. Right eccentric and dense mural nodule. b) Papilloma. Anterior lobulated isodense nodule in distal trachea. c) Viral Supraglottitis. Markedly swollen mucosa that obliterates the tracheal lumen. d) Allergic Angioedema. Thickening of the aryepiglottic folds bilaterally is present. e) Subglottic Granuloma in a patient with history of longterm intubation shows an eccentric posterior mucosal thickening that narrows the posterior tracheal lumen. f) Stenosis post tracheostomy in a patient with history of longterm intubation. Eccentric soft-tissue thickening thickening that narrows the posterior tracheal lumen is seen.

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Fig. 5: Unilateral orbital GPA granuloma in 2 different patients. a) Axial and b) Coronal CT using soft tissue windows show left orbital soft-tissue mass-like lesion with mild proptosis. There is opacification of anterior and posterior ethmoids. Note the large defect of the nasal septum (*). (c,d,e) Axial CT scans in a different patient with GPA with subglottic stenosis and associated orbital pseudotumor. There is a medial orbital intraconal mass in the left orbit extending from an ethmoid sinonasal granuloma. Note ethmoid septae and nasal septum destruction in (d) and the sclerotic bony changes in both maxillary sinuses (e).

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Fig. 6: Differential diagnosis of GPA orbital involvement. a) Orbital inflammatory pseudotumor. MRI T2-weighted image shows enlargement of the superior, medial and inferior recti muscles (white arrowheads), with hyperintense signal, loss of normal intraconal fat signal. b) Breast metastases. Coronal T1 post contrast with fat saturation shows a heterogeneously enhancing lesion infiltrating the fat. c) Lymphoma. MRI T2-weighted image shows enlargement of both lacrimal glands (*). d) Leukemia. Coronal T1-weighted fat-suppressed, gadolinium-enhanced image showing bilaterally symmetrical diffusely enlarged lacrimal glands (*) with intense homogenous enhancement. e) Amyloidosis. CT shows an expansile, infiltrating masses with calcifications in a patient with a globe prosthesis.

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**Fig. 7:** Petrous apicitis in a patient with GPA. a,b) Axial and coronal gadolinium-enhanced-fat-suppressed T1weighted MR images show diffuse enhancement of right mastoid cells and middle ear, anterior petrous apex and clivus. There is also a focal rim-enhancing fluid collection in the anterior petrous apex compatible with an abscess, (arrowhead). In figure a, there is destruction of the nasal septums.

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Fig. 8: GPA-related brain involvement. a) Axial T2 weighted image b) Axial T2 FLAIR c) DWI and d) ADC map. There is left frontal sinus inflammatory disease (arrow) extending intracranially and showing restricted diffusion in the left frontal lobe compatible with infarction. Differential diagnosis was fungal paranasal sinus infection with extension into the brain parenchyma.

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Fig. 9: Patient with GPA related cerebral small-vessel vasculitis. a) Axial T1 weighted post contrast image shows punctiform/linear enhancement in the centra semiovale. b) Sagittal T2 weighted image shows focal areas of abnormal high signal intensity, predominantly in the white matter. c) Axial CT scan shows complete erosion of nasal structures.

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**Fig. 10:** DSA image of same patient shown in previous slide obtained after ICA injection shows multiple arterial narrowings (yellow ovals).

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Fig. 11: Patient with GPA-related cerebral small-vessel vasculitis. a) Axial FLAIR MRI shows area of hyperintensity within the subcortical white matter of the left parietal lobe suggesting a previous infarction. b) Note the large septum defect characteristic of GPA sinonasal disease in this patient.

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**Fig. 12:** (a,b,c ) Axial, sagital, coronal planes of brain MRI T1-post gadolinium images showing an infiltrative mass involving the hypothalamus with extension into the infundibulum.

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Fig. 13: Differential diagnosis of GPA pituitary involvement. a) Sarcoidosis, b) Metastasis, c) Leukemia and d) IgG4 hypophysitis. Post-contrast sagittal T1 MRI images show suprasellar masses involving the pituitary gland, stalk and hypothalamic in various degrees. e,f) Lymphocytic hypophysitis, Post-contrast sagittal T1 MRI images in 2 different patients demonstrate a homogenous avidly enhancing enlarged pituitary glands with thickening of their pituitary stalks. g) Germinoma. Again, a non specific infiltrative mass in the gland and its stalk are seen. h) After treatment of melanoma with monoclonal antibodies there is enlargement of the gland.

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Fig. 14: GPA related chronic hypertrophic pachymeningitis. Coronal T1 post Gad sequence shows dural thickening and enhancement along the left frontoparietotemporal convexity, tentorium and cerebellopontine angle.

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Fig. 15: Hypertrophic pachymeningitis differential diagnosis. a) Intracranial hypotension. b) Post shunt dural fibrosis. c) Dural prostate metastases with involvement of the right frontal skull bone. d) Smooth dural enhancement is seen but there is an extra-axial right posterior frontal mildly enhancing mass-like lesion. e) Diffuse nodular dural enhancement is present. f) Significantly thick/nodular dural enhancement is present with extension into the venous sinuses. g) Extra-axial mass-like lesions are present (there is an incidental left frontal DVA).

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Conclusion

GPA is a multi organ disease that frequently affects head and neck with typical findings in the sinonasal cavities. However, involvement of the orbit and CNS is less frequent and findings are less specific. The radiologist should recognize the CNS imaging manifestations of GPA because it is associated with a refractory course requiring aggressive immunosuppressive therapy. Unfortunately there are no reliable pathognomonic imaging features that suggest the right diagnosis but certain patterns of disease may lead to the diagnosis GPA. An accurate clinical history, laboratory studies and imaging findings are all necessary to achieve the correct diagnosis.
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References


