Unique Imaging Findings of Neurologic Phantosmia Following Pfizer-BioNtech COVID-19 Vaccination: A Case Report

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Abstract: Olfactory dysfunction related to SARS-CoV-2 infection and COVID-19 disease is now well established in the literature. In December 2020, the FDA approved the Pfizer-BioNTech and Moderna vaccines for use in preventing COVID-19 in the United States. To the best of our knowledge, this is the first report of a phantosmia post-Pfizer COVID-19 vaccination, with positive magnetic resonance imaging radiographic findings in a patient with documented absence of infection by SARS-CoV-2 virus or concomitant sinonasal disease.

Key Words: COVID-19 vaccine, magnetic resonance imaging, olfactory dysfunction, phantosmia

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Disorders of smell, including anosmia, phantosmia, and dysgeusia, are well-documented complications of SARS-CoV-2 infection and COVID-19 disease.[1–4] COVID-19 olfactory dysfunction (OD) often occurs suddenly is transient and recovers within several weeks.[5,6] Radiographically, COVID-19 OD may demonstrate altered olfactory bulb signal on T1 with punctate hyperintensities thought to represent microhemorrhages, olfactory tract, and bulb T2 and FLAIR hyperintensity likely edema from infectious or inflammatory change and clumping of olfactory nerve filia on sagittal high-resolution T2-weighted imaging, with resolution of findings as olfactory function normalizes.[6–9] In December 2020, the FDA approved the Pfizer-BioNTech and Moderna COVID-19 vaccines for prevention of COVID-19.[10] Vaccine clinical trial-reported side effects included injection site pain, myalgias, fever, fatigue, and anaphylactic shock.[10–13] Additional case reports of postvaccine side effects included Guillain-Barre syndrome,[14] and rarely (n = 12) reported cases of a severe allergic response, possibly from polyethylene glycol within the vaccines.[15] To date, there are no reports of OD after COVID-19 vaccination. This report details clinical and radiographic features of a smoke smelling phantosmia following Pfizer COVID-19 vaccination, with reverse transcription polymerase chain reaction (PCR) confirmed absence of SARS-CoV-2 viral infection.

CASE

A 57-year-old woman presented to the emergency department complaining of constantly ''smelling smoke'' and headaches after her second dose of Pfizer's COVID vaccine. The patient reported a strong reaction to the first vaccine dose, feeling weak, fatigued, with random episodes of ''smelling smoke.'' After receiving the second Pfizer COVID, the intermittent phantosmia of ''smelling smoke'' became constant and associated with hyposmia to additional odorants and was affecting her quality of life. She denied any parosmia, issues with taste, nasal congestion, rhinorrhea or post-nasal drip, and had no history of sinus infections. Medications included a prescription for Flonase recommended by neurology for the phantosmia occurring after the first vaccination. COVID-19 PCR testing was negative. Vital signs and physical examination by otolaryngology revealed unremarkable cranial nerves II–Xll, with no facial weakness or asymmetry. Motor examination of upper and lower extremities was within normal limits. Laboratory values demonstrated: WBC 5.49, Hgb 13.8, hematocrit 41.6, which were unremarkable. There was an elevated serum cholesterol 236 mg/dL, and LDL 122 mg/dL. A CT angiography (CTA) of the head and neck and a magnetic resonance imaging (MRI) (3 Tesla) of the brain with dedicated T1- and T2-weighted sequences of the olfactory tract and bulbs, with and without gadolinium and fat saturation, were obtained.

RESULTS

Head CT and CTA imaging were obtained on Optima GE CT660 128 slice multidetector CT scanner. For the head CT a dedicated field of view (DFOV) 25 × 27.4 cm, axial 5 mm slices, CTA was obtained after 70 cm^3 intravenous iodinated Omnipaque 300, with DFOV 25.4 × 27.9 cm, with 0.63 mm axial slices, with multiplanar 3D reconstruction using 3D Carestream Software. MRI dedicated brain and olfactory bulb imaging was obtained on a 3 Tesla MRI unit (3 Tesla Prisma MRI unit, Siemens, Erlangen, Germany), using a 32-channel head coil. Ultra-high resolution T2-space axial images were obtained through the olfactory bulbs with DFOV 17.3 × 18.9 cm (repetition time [TR]): 1400 ms, echo time (TE): 152 ms, slice thickness 1 mm. Axial and coronal T2 thin section fat-saturated sequences with attention to olfactory bulbs were obtained, axial T2 with DFOV 14.7 × 15.8 cm (TR): 3000 ms, TE: 89 ms, slice thickness 3 mm, coronal with DFOV 8.1 × 8.7 cm (TR): 4760 ms, TE: 89 ms, slice thickness 3 mm. Axial and coronal T1 with attention to the olfactory nerves were obtained precontrast with axial DFOV 18 × 19.4 cm (TR): 469 ms, TE: 8.2 ms, slice thickness 3 mm, and coronal with DFOV 9.0 × 9.7 cm (TR): 425 ms, TE: 8.4 ms, slice thickness 3 mm, and postintravenous administration of 8 cm^3 Gadavist gadolinium with fat-saturated axial and coronal T1 attention to olfactory nerves axial DFOV 18 × 19.4 cm (TR): 659 ms, TE: 7.6 ms, slice thickness 3 mm, and coronal with DFOV 18 × 19.4 cm (TR): 609 ms, TE: 8.4 ms, slice thickness 3 mm, and thin section axial MPRAGE postcontrast whole brain images with DFOV 17.7 × 19 cm (TR): 1520 ms, TE: 2.66 ms, slice thickness 1 mm, reconstructed into coronal and sagittal planes. Brain imaging included Sag T1, axial T1, T2, FLAIR, SWI, DWI, with epiplanar DWI with attention to olfactory bulbs and tracts, with axial DFOV 22 × 23.7 cm (TR): 3930 ms, TE: 45 ms, slice thickness 3 mm, and coronal with DFOV 9.0 × 9.7 cm (TR): 425 ms, TE: 8.4 ms, slice thickness 2.5 mm, to reduce skull base artifact.

Noncontrast head CT was unremarkable, there was no intracranial hemorrhage, mass, or shift. The sinonasal cavities and mastoids

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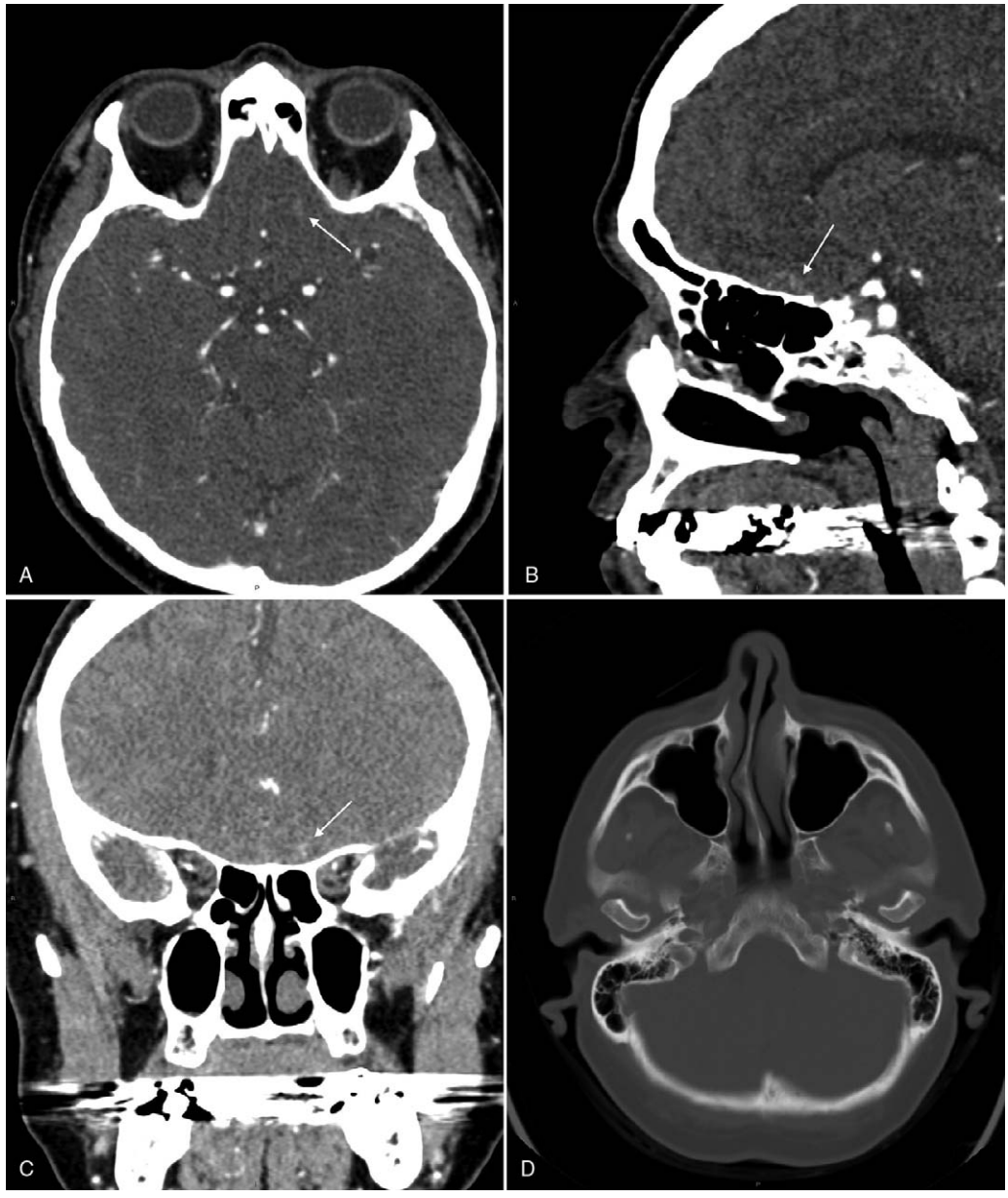

FIGURE 1. A–D, CTA in 57-year-old woman with smoke smelling phantosmia (A, axial, B, sagittal, C, coronal) and axial bone window CT (D). CTA postcontrast demonstrates faint enhancement left olfactory tract (white arrow). Axial bone window CT (D) rightward nasal septal deviation and right osseous spur, paranasal sinuses were clear without fluid levels, retention cysts, or polyps.

were unremarkable with minimal ethmoid mucosal thickening and no air fluid levels, no retention cysts or polyps were identified. Postcontrast CTA and T1 axial postgadolinium demonstrated faint left greater than right olfactory tract enhancement, bone windows demonstrated rightward nasal septal deviation (Fig. 1A–D). Three tesla MRI axial T1 postcontrast images revealed left greater than right olfactory bulb and tract enhancement (Fig. 2A–C). On axial T2 and FLAIR images there was T2 signal hyperintensity along the left olfactory bulb and bilateral olfactory tracts suggestive of edema (Fig. 3A–C). Thin section coronal T2 fat-saturated imaging revealed asymmetric enlargement and increased T2 hyperintensity in the left olfactory bulb and tract extending posteriorly (Fig. 4A–C). On sagittal thin section T2-weighted imaging the olfactory nerve filia were thickened and clumped (Fig. 5). The ostiomeatal complexes, frontal, and sphenoethmoidal recesses were clear. There was inferior rightward nasal septal deviation with bilateral middle turbinate concha bullosa with minimal ethmoid sinus mucosal thickening, there were no air-fluid levels, polyps, or retention cysts.

DISCUSSION

SARS-CoV-2, similar to the SARS-Co-V, infects cells via the viral capsid spike protein (S) interacting with the angiotensin-converting enzyme-2 (ACE-2) receptor protein located on the target cell surface.[16,17] The interaction involves cleavage of the S protein,

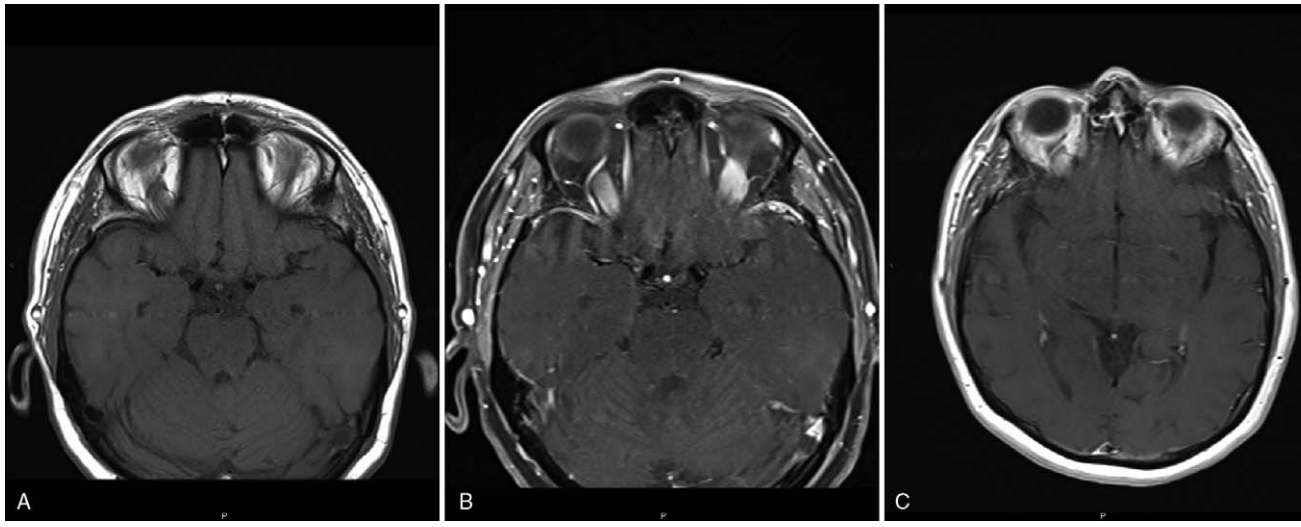

FIGURE 2. A–C, Axial 3T MRI T1-weighted postgadolinium axial images demonstrating enhancement of the left greater than right olfactory bulb and bilateral olfactory tracts.

thought to be via the cell surface protease transmembrane serine protease 2 (TMPRSS2), additional proteases such as cathepsin B and L may also be used.[17] The nasal cavity contains respiratory epithelium that humidifies air, composed of basal cells, ciliated cells, secretory goblet cells and brush microvillar cells, and olfactory epithelium (OE). The OE used for smell detection contains olfactory receptor neurons and overlies the ethmoid bone cribriform and cranial superior turbinates. The olfactory sensory receptor neurons (OSNs) are grouped together within bundles with interleaved glial cells called olfactory ensheathing cells. The bipolar shaped receptor neurons are within intranasal OE mucus with hairy chemosensitive dendritic cilia receptors that interact with odorant molecules. The unmyelinated axons reach olfactory bulbs via the bony cribriform plate sieve-like openings, allowing extracranial to intracranial transfer of olfactory sensory information via the olfactory nerve filia, which can be identified on ultra–high-resolution T2-weighted images.[6,18] The neuron bundles form rounded olfactory glomeruli that synapse with second-order neuronal mitral cells in the olfactory bulb.[18] The mitral cell myelinated axons are in the olfactory tract and split into medial, intermediate and lateral striae before reaching the perforated substance.[18] The OSNs are supported by sustentacular cells (SUS) that phagocytose potentially toxic material and maintain salt and water balance.[19,20] The mitral valve cells and mucus secreting Bowman gland (BG) cells maintain olfactory epithelial balance and function, along with globose basal cells that regenerate the OSNs during epithelial turnover, and horizontal basal cells (HBCs), that have reserve stem cells if tissue is damaged.

Research on mouse and human tissue revealed subsets of olfactory epithelial cells namely the OE SUS, HBCs, and BG cells that express ACE-2 CoV-2 receptor protein and S protein protease TMPRSS2, with genetic expression at levels similar to lung tissue.[21–25] Experimental animal mouse models have demonstrated that

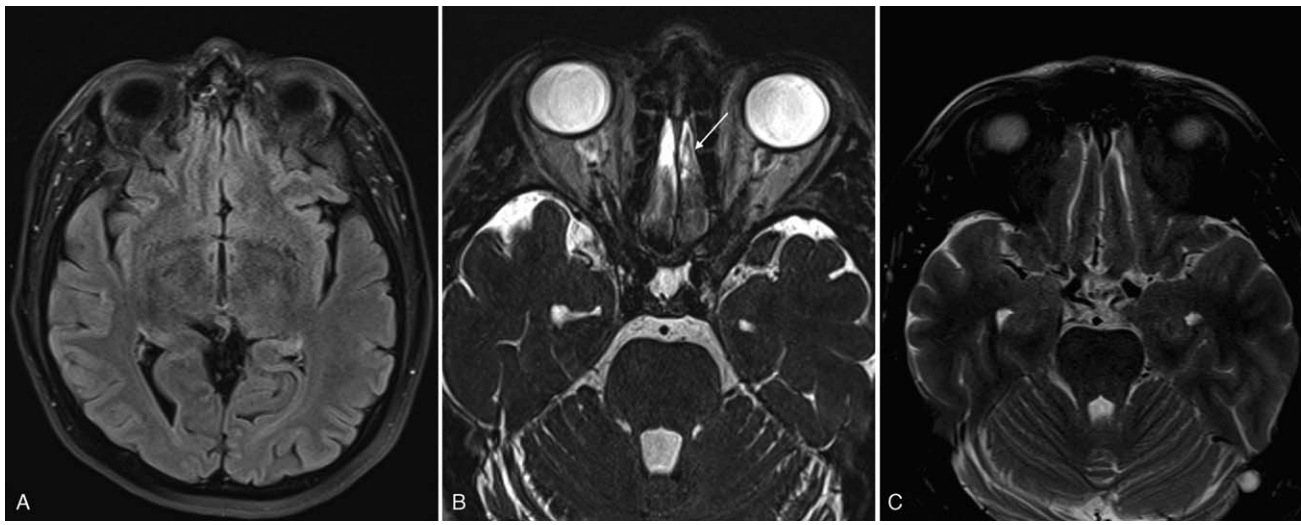

FIGURE 3. A–C, Axial 3T MRI (A, FLAIR, B, high-resolution thin section T2, C, axial T2 with fat saturation) with FLAIR and T2 hyperintensity in olfactory bulbs and tracts (white arrows).

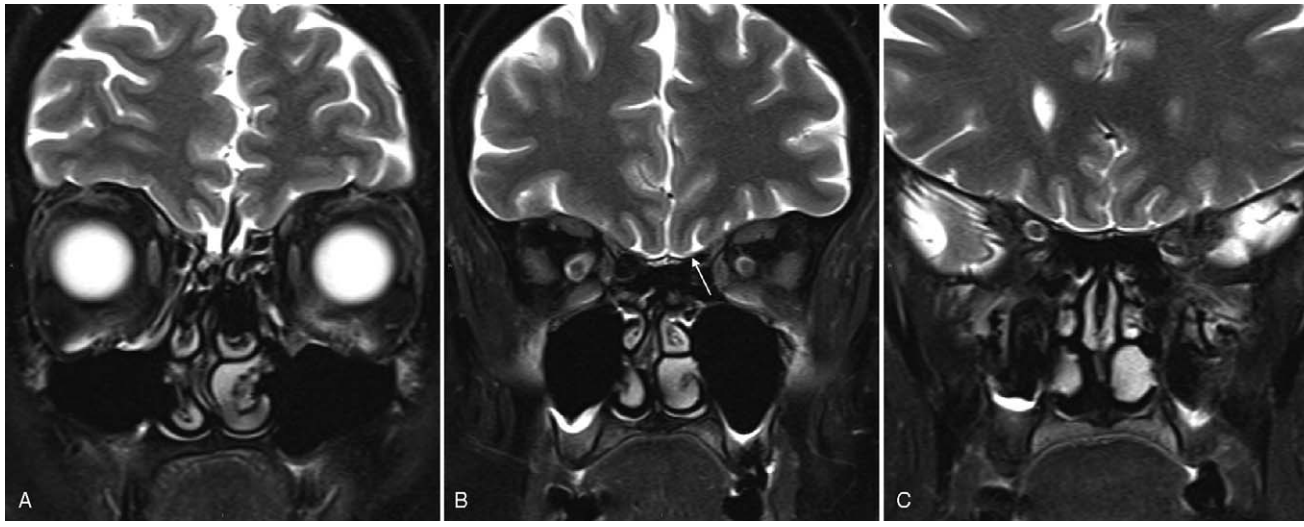

FIGURE 4. A–C, Coronal 3T MRI, T2 fat-saturated images with T2 hyperintensity left olfactory bulb (A) asymmetric T2 hyperintensity and enlargement left olfactory tract (B, C) (white arrow).

SARS-CoV-2 viral spike proteins attach to ACE-2 receptors in the olfactory epithelial support and to perivascular cells, leading to infectivity in the olfactory bulb.[21–24] Imaging of patients with OD in the setting of COVID-19 infection suggests that viral SARS-CoV-2 attachment to olfactory epithelial and perivascular ACE-2 receptors may represent the site of viral entry and intracranial access, leading to microvascular disruption, microhemorrhages, and resultant olfactory bulb and tract edema, and in certain cases olfactory tract encephalomalacia and gliosis.[6–9]

This article presents a unique case of ''smelling smoke'' phantosmia occurring after Pfizer COVID vaccination, with documented negative SAR-CoV-2 PCR. Radiographic findings included olfactory bulb and tract enhancement and T2 and FLAIR hyperintensity, likely edema with clumping of the olfactory nerve filia on high-resolution thin section sagittal T2-weighted imaging (Figs. 1–5). The Pfizer-BioNtech vaccine, tozinameran, or brand name Comirnaty is an mRNA (BNT162b2) vaccine approved by the FDA via emergency use authorization on December 11, 2020. The vaccine is given in two 0.3 mL doses via intramuscular deltoid route, 21 days apart, and has shown to be 95% effective in preventing SARS-CoV-2 infection.[10,12] The vaccine is formulated in lipid particles enabling delivery of RNA into host cells to express the SARS-CoV-2 S antigen and elicits an immune response to the S antigen, protecting against COVID-19.[10–12] Although the etiology of smoke phantosmia occurring after vaccination is unknown, the imaging manifestations in this patient are similar to those with COVID-19 anosmia, suggesting an immune response in the OE may be elicited involving the olfactory epithelial cells expressing the ACE-2 receptor and the S protein protease TMPRSS2 on the SUS, HBCs, and BG cells. The vaccine inflammatory response may result in an inflammatory mechanism occurring when SARS-CoV-2 attaches to olfactory epithelial ACE-2 receptors with resultant edema and clumping of olfactory filia, as seen on sagittal high-resolution T2-weighted imaging (Fig. 5). As in patients with COVID-19 OD with phantosmia or anosmia, it remains to be established whether these effects on olfactory function are temporary or long lasting.[26]

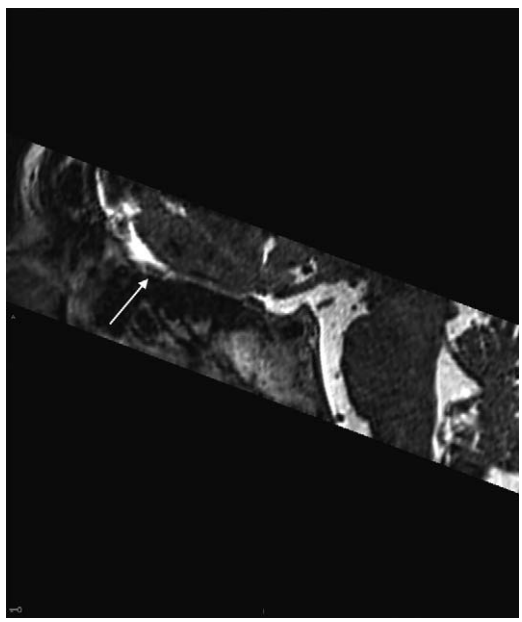

FIGURE 5. Sagittal 3T MRI high-resolution T2 image with thickened clumped left olfactory nerve filia (white arrow).

CONCLUSIONS

To the best of our knowledge, this is the first report of ''smelling smoke'' phantosmia post Pfizer COVID-19 vaccination with MRI radiographic findings, including olfactory tract enhancement, edema, and clumping of olfactory nerve filia, on high-resolution sagittal T2 MRI. The patient was negative for SARS-CoV-2 infection on PCR and underlying sinonasal disease. Imaging manifestations included olfactory bulb edema, enhancement, and thickened clumped olfactory nerve filia, findings reported in documented COVID-19 anosmia.[6,7] The etiology of phantosmia and the radiographic findings may reflect an inflammatory response to the viral S antigen via ACE-2 CoV-2 receptor protein and the S protein protease TMPRSS2 pathways. Awareness of this potential postvaccination finding, and imaging manifestations, may improve understanding of SARS-CoV-2, ACE-2, and S protein protease TMPRSS2 interactions, vaccine-induced sensitivity, and SARS-CoV-2 pathophysiology.

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