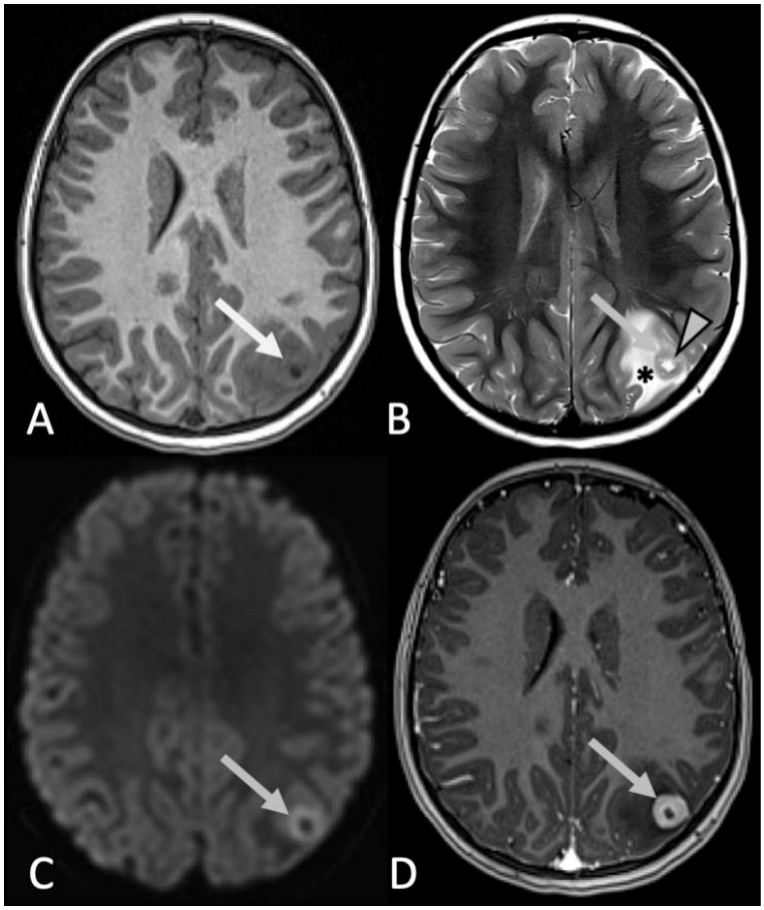
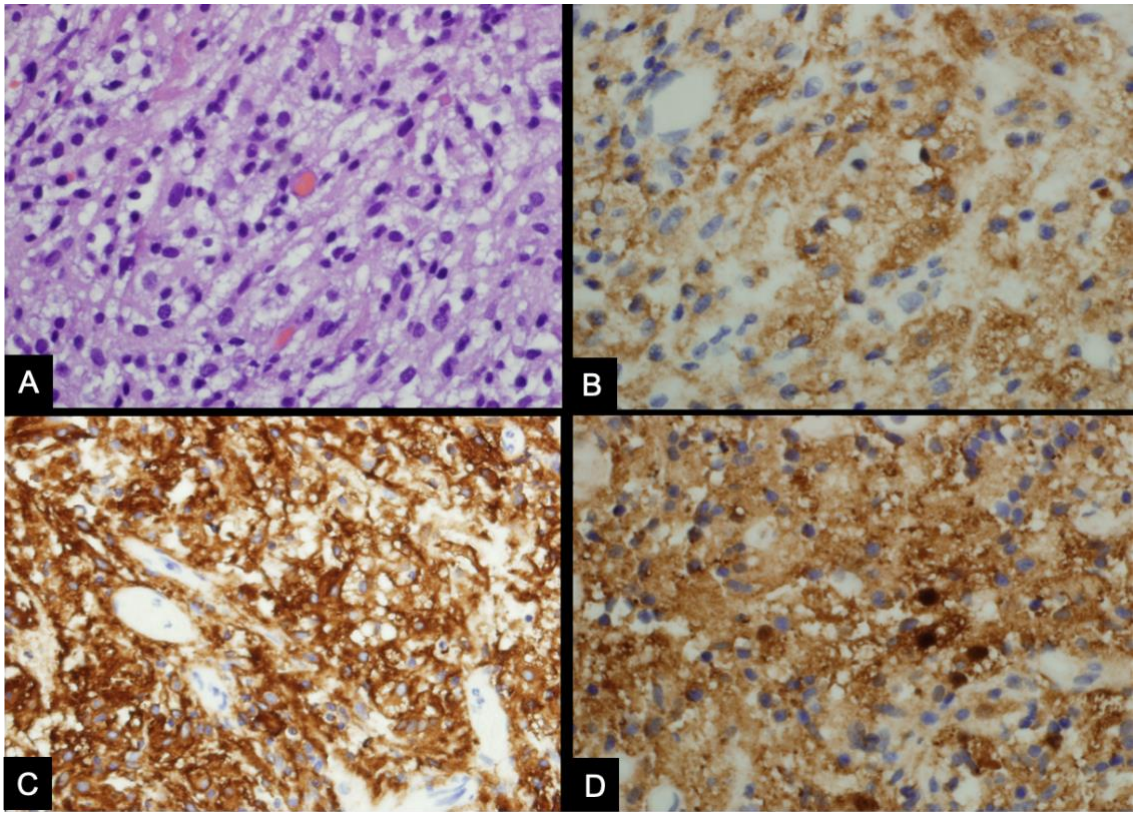


Supplementary Figure 1: Brain MR images obtained in a 4-year-old girl with pathology-proven unifocal JXG. The patient presented with new onset seizures. (A) axial T1-weighted image, (B) axial T2-weighted image, (C) axial DW image and (D) axial T1+C-weighted image. Brain MRI depicts a round peripherally located unifocal lesion in the left parietal lobe (arrows in A-D) with central necrosis (arrowhead in B) and perilesional edema (asterisk in B). Compared to cortical gray matter, the lesion is T1-isointense (A), T2-isointense (B), shows restricted diffusion (C; matching ADC map not shown) and marked contrast enhancement of the non-necrotic solid portion (D).



Supplementary Figure 2: Juvenile xanthogranuloma involving the CNS: histopathologic and immunohistochemical features. (A) Prominent histiocytes with markedly vacuolated cytoplasm (H&E, original magnification 400x). (B) Diffuse cytoplasmic staining of lesional cells with CD163 (original magnification 400x). (C) Diffuse cytoplasmic staining of lesional cells with factor XIIIa (original magnification 400x). (D) Diffuse cytoplasmic staining of lesional cells with fascin (original magnification 400x).

Supplementary Table 1: Demographics and further clinical information of 14 patients with CNS JXG

Patient	Sex	Age at biopsy/diagnosis (in months)	Initial clinical presentation	Involved organ system(s)	Histological diagnosis	Clinical Molecular Data	Clinical outcome
1	Female	78	Headaches	CNS	JXG	CDK2NA loss, BRAF-V600E negative	Alive
2	Female	220	Polyuria, polydipsia, headaches, amenorrhea	CNS (only pituitary stalk)	JXG	BRAF-V600E negative	Alive
3	Female	90	Headaches, vomiting	CNS	Mixed JXG/RDD	ALK1+	Alive
4	Female	4	Hearing loss, unilateral facial palsy	CNS	JXG	BRAF-V600E negative, ALK negative	Alive
5	Female	52	Seizure	CNS	JXG	No mutations on targeted panel	Alive
6	Female	54	Ataxia, tremor, altered speech	CNS, skin	JXG	BRAF-V600E+	Alive
7	Male	128	Headaches, esotropia	CNS	JXG	No mutations on targeted panel	Alive
8	Female	52	Rash	CNS (including pituitary stalk), skin, conjunctive, eye globe	JXG	NF1 mutation (heterozygous, missense exon 21)	Alive
9	Male	95	Rash, limping	CNS (including pituitary gland and stalk), skin, bone	Mixed LCH/JXG	BRAF-V600E+	Alive
10	Male	2	Seizures	CNS	JXG	Not available	Alive
11	Male	43	Strabismus	CNS, skin, bone	JXG	Not available	Alive
12	Male	14	Apparent life threatening event (ALTE)	CNS, skin, bone, lungs, kidneys, lymph node	JXG	Not available	Alive
13	Female	224	Rash	CNS, skin, soft tissue (pharynx)	JXG	CDK2NA loss, BRAF-V600E negative	Deceased
14	Male	143	Otalgia, hearing loss, facial nerve palsy, headaches	CNS, PNS	JXG	No mutations on WES	Alive

Supplementary Table 2: Demographics, location, size and imaging features of 14 patients with CNS JXG

Patient	Sex	Age at imaging (months)	Neuroradiologic pattern	Location	Max. diameter at presentation (cm)	Pituitary bright spot	Perilesional edema	Cystic component	Necrosis	Blood products	T1WI	T2WI	ADC	Contrast enhancement on T1+C	Additional CT available (solid portion)
1	Female	78	Unifocal	Cerebrum	4.8	Yes	Yes	No	Yes	Yes	Isointense	Isointense	ADC hypointense	Heterogeneous	Hyperdense
2	Female	220	Unifocal	Infundibulum	0.8	NA	No	No	No	NA	NA	Hyperintense	NA	Homogeneous	NA
3	Female	90	Unifocal	Cerebellum	2.9	Yes	Yes	No	No	Yes	Isointense	Iso- to hyperintense	ADC hypointense	Heterogeneous	NA
4	Female	1	Unifocal	Pons	2.9	Yes	Yes	Yes	Yes	No	Hypo- to isointense	Hypo- to isointense	ADC hypointense	Homogeneous	NA
5	Female	52	Unifocal	Cerebrum	1.3	Yes	Yes	No	Yes	No	Isointense	Isointense	ADC hypointense	Heterogeneous	Hyperdense
6	Female	52	Multifocal	Cerebrum, cerebellum, brachium pontis, midbrain, pons, medulla, corpus callosum, infundibulum, septum pellucidum	0.9	Yes	Yes	No	No	No	Hyperintense	Isointense	ADC isointense	Homogeneous and no	NA
7	Male	121	Multifocal	Cerebrum, cerebellum, brachium pontis, pons, corpus callosum, pituitary gland, infundibulum, hypothalamus, optic chiasm/apparatus	3	Yes	Yes	No	Yes	Yes	Hyperintense	Hyperintense	ADC hypointense	Larger lesions: Heterogeneous Smaller lesions: Homogeneous	NA
8	Female	53	Multifocal	Cerebrum, cerebellum, brachium pontis, pons, infundibulum, hypothalamus	0.8	Lost	Yes	No	No	No	Isointense	Hyperintense	ADC isointense	Homogeneous	NA
9	Male	97	Multifocal	Cerebrum, cerebellum, pons, vermis, pituitary gland, infundibulum	2.7	Lost	No	No	No	NA	Hyperintense	Hyperintense	NA	Heterogeneous	NA
10	Male	2	Multifocal	Cerebrum, midbrain, optic chiasm/apparatus	2.4	Yes	Yes	Yes	No	No	Isointense	Isointense	ADC hypointense	Larger lesions: Heterogeneous Smaller lesions: Homogeneous	Hyperdense
11	Male	43	Multifocal	Cerebrum, cerebellum, pons	1.3	Yes	Yes	No	No	No	Hyperintense	Iso- to hyperintense	NA	Homogeneous	Hyperdense
12	Male	15	Multifocal	Cerebrum, cerebellum, corpus callosum, intraventricular, septum pellucidum	1.8	Yes	Yes	No	Yes	No	Isointense	Isointense	ADC hypointense	Homogeneous	NA
13	Female	227	Multifocal	Cerebrum, pons, pituitary gland, infundibulum	0.9	Lost	Yes	No	No	No	Isointense	Iso- to hyperintense	ADC isointense	Homogeneous	NA
14	Male	128	Multifocal with leptomeningeal brain and spine involvement	Cerebrum, hypothalamus, bilateral internal auditory canals, bilateral Meckel's cave, leptomeningeal (brain, spine)	3.8	Yes	NA	No	Yes	NA	NA	NA	NA	Heterogeneous	NA