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An unusual pAIR: Anti-PKM2 antibody and occult pancreatic adenocarcinoma

Meredith P. Spitz [a], David R. Anderson [b], Tamara R. Vrabec [a,*]

[a] Geisinger Eye Institute, Danville, PA, USA
[b] Retina Consultants of Minnesota, Edina, MN, USA

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ABSTRACT

Purpose: To describe the clinical, laboratory and multimodal imaging findings in paraneoplastic autoimmune retinopathy (p-AIR) associated with anti-pyruvate kinase M2 antibody (anti-PKM2) and occult pancreatic adenocarcinoma.

Observations: A 70 year old male with blurred vision, nyctalopia and concurrent difficulty with glucose control had retinal vascular attenuation and diffuse punctate pigment clumping in both eyes. Multimodal imaging demonstrated corresponding stippled hypofluorescence on fluorescein angiography, stippled hyper-autofluorescence and a hyperautoflourescent macular ring with fundus autofluorescence, and focal hyper-reflectivity at the level of the RPE-Bruch's membrane complex with diffuse loss of outer retinal layers on ocular coherence tomography. In addition, diffuse ganglion cell loss and severe visual field constriction were present. Genetic testing for retinitis pigmentosa was normal. Screening for anti-retinal antibodies was positive for only anti-PKM2. Systemic evaluation revealed previously undiagnosed adenocarcinoma of the pancreas.

Conclusions and importance: Anti-PKM2 in the setting of autoimmune retinopathy may be associated with occult pancreatic cancer. The diagnosis of pAIR should be considered and systemic investigation for occult malignancy initiated even in the absence of more commonly associated anti-retinal antibodies.

1. Introduction

Paraneoplastic autoimmune retinopathy (p-AIR) is a clinical syndrome defined by the association of serum auto-antibodies directed against retinal antigens shared by non-ocular tumors in persons with sudden, progressive loss of visual acuity and visual field. Clinical variants, cancer associated retinopathy (CAR),[1,2] melanoma associated retinopathy (MAR)[3] and bilateral diffuse melanocytic proliferation (BDUMP)[4] may be distinguished by clinical findings and multimodal imaging.[5]

One previous report of presumed CAR in a patient with vision loss, normal fundus, ellipsoid zone loss and ampullary pancreatic carcinoma did not include serum anti-retinal autoantibodies.[6] We are unaware of previous reports of p-AIR with associated anti-PKM2 antibodies secondary to occult pancreatic adenocarcinoma and could find no reference to it in a computerized search (PubMed, unrestricted date range).

2. Case report

A 70-year-old male with past medical history of type 2 diabetes, hypertension and diverticulosis presented with four months of intermittent blurry vision, glare around lights and foggy vision in low light in both eyes (OU). His past ocular history included cataract extraction OU, epiretinal membrane (ERM) peel OD, and peripheral laser photocoagulation OU. He denied family history of vision loss but noted concurrent difficulty controlling his glucose and an unintentional thirty-pound weight loss.

Best corrected visual acuity was 20/60 with pinhole to 20/50 OD and 20/25 OS. Intraocular pressures were 14 mm hg OU and pupils were round and equally reactive to light without afferent pupillary defect. Confrontational visual fields were constricted OU. Slit lamp biomicroscopy revealed severe punctate keratitis and pseudophakia OU but no vitreous cells. Dilated fundoscopy was remarkable for severely attenuated retinal vasculature, peripheral depigmentation and diffuse punctate hyperpigmentation OU (Fig. 1A) with numerous peripheral laser photocoagulation scars OU.

* Correspondence author. Geisinger Eye Institute, 16 Woodbine Lane, Danville, PA, 17821, USA.
E-mail address: tvrunning@aol.com (T.R. Vrabec).

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FAF revealed increased autofluorescence in the macula with a hyperautofluorescent ring centered around the fovea as well as more peripheral punctate hyperautofluorescence on a hypo-autoflourescent background which corresponded to the pigmented lesions (Fig. 1B). IVFA demonstrated a coarsely stippled pattern of hypofluorescence on a hyperfluorescent background which corresponded to the pigmented fundus lesions (Fig. 1C). There was mild late hyperfluorescence of the optic disc and macula OU which was greater OD due to persistent ERM. OCT showed severe attenuation of outer retinal layers with photoreceptor cell loss OU. Focal deposits at the level of the RPE Bruch's membrane complex correlated to pigmented fundus lesions (Fig. 1D). There was RNFL thinning of both optic nerves and ganglion cell loss OU. Humphrey visual fields were severely constricted and depressed OU (Fig. 2) The patient no family history of retinitis pigmentosa or other inherited retinal disease. Genetic screening using sequence and del/dup analysis (BluePrint Genetics, My Retina Tracker Program Panel) did not detect any known disease causing or rare variants that could explain the patient's phenotype. The patient declined electrophysiology evaluation.

The patient was up to date on cancer screenings including prostate specific antigen and colonoscopy. An antiretinal antibody panel including antibodies to carbonic anhydrase II, HSP27, aldolase, enolase, arrestin, tubulin, PKM2 and GAPDH (glyceraldehyde 3-phosphage dehydrogenase) (Ocular Immunology Laboratory, Casey Eye Institute, Oregon Health Science University) was positive for only anti-PKM2. Carbohydrate antigen (CA 19-9) was elevated (235 U/ml, normal <37 U/ml)). A CT scan of chest, abdomen and pelvis showed a spiculated mass at the head of the pancreas with local lymphadenopathy (Fig. 3). Fine needle aspiration biopsy confirmed pancreatic adenocarcinoma. Because the tumor (Stage III T3, N1, M0) was in close proximity to the superior mesenteric vessels, therefore inoperable, the patient was managed with ongoing neoadjuvant folfirinox. Fourteen months after presentation, the patient reported vision was unchanged. Visual acuity was unchanged in both eyes. FAF demonstrated mild reduction and constriction of autofluorescence (Fig. 4).

3. Discussion

Pyruvate kinase is a tetrameric glycolytic enzyme. The dimeric isoform, PKM2, is upregulated and may be identified in plasma during tumorigenesis. It can enter the nucleus to promote angiogenesis[7] and shift glucose metabolism toward aerobic glycolysis in cancer cells in order to promote rapid cell division and prevent Ca2+-dependent cell death.[8] Abundant in photoreceptors.[9,10] PKM2 regulates aerobic glycolysis which accounts for over 80% of retina glucose metabolism.[10] PKM2 is also expressed by pancreatic islet cells[11] as well as RPE cells albeit at lower levels than in photoreceptors.[12] Anti-PKM2 antibodies, formed in response to antigens expressed or formed by the occult pancreatic adenocarcinoma, may also have simultaneously targeted pancreatic islets cells and photoreceptors resulting in apoptosis evident as outer retinal thinning on OCT with vision loss and concurrent erratic serum glucose.

Multimodal imaging revealed a parafoveal hyperautoflourescent ring, a nonspecific finding described in both CAR[13] and retinitis pigmentosa.[14] However the punctate pattern of extramacular hyper-autofluorescence is not typical of either[13,15]. Compared to imaging in BDUMP including a previously reported case associated with pancreatic carcinoma,[4,16] the FAF and IVFA patterns in this case are distinct. FAF demonstrates punctate bright areas on a dark background, and IVFA demonstrates corresponding dark spots on a bright background both of which correlate to clinically apparent pigment clumps. Unlike BDUMP as described by Gass, our patient did not have annular red patches, pigmented or non-pigmented uveal melanocytic tumors or exudative retinal detachment.[4]

FAF reflects lipofuscin distribution and viability of photoreceptors

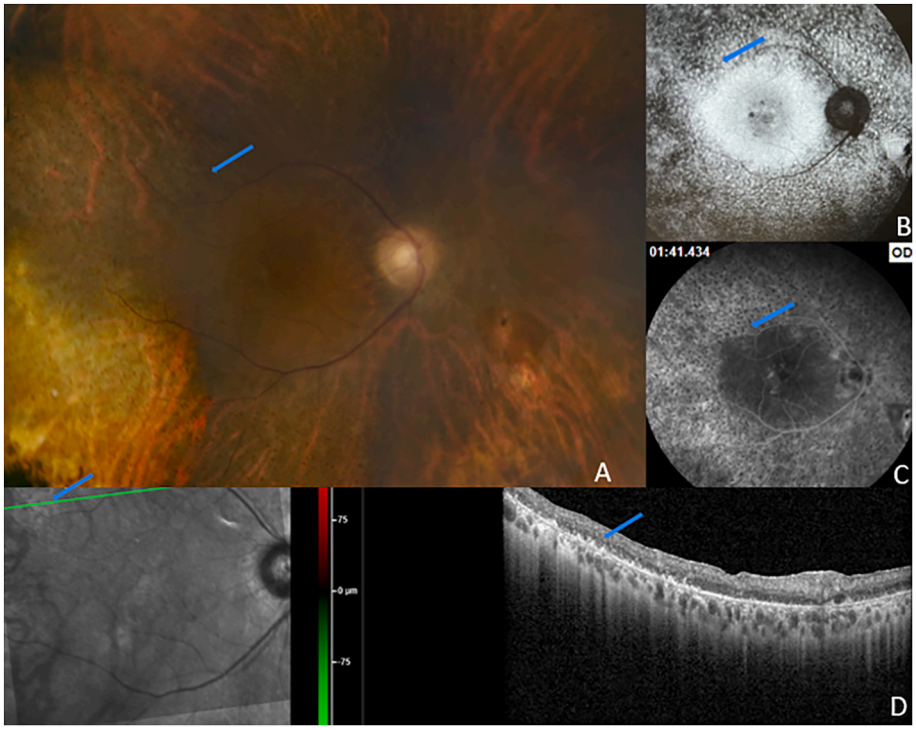

Fig. 1. Clinical appearance and multimodal imaging.
Fundus photograph demonstrates attenuated retinal vasculature. Diffuse punctate hyperpigmentation is present throughout (1a, arrow). FAF shows hyperautofluorescence ring centered around the fovea and widespread punctate hyper-autofluorescence which corresponded with the clinically evident pigmented lesions (1b, arrow). Fluorescein angiography reveals coarsely stippled pattern of hypofluorescence which corresponds to the pigmented fundus on a hyperfluorescent background (1c, arrow). Attenuation of outer retinal layers with photoreceptor cell loss is evident on OCT OU. Line scan demonstrates deposits at the level of the RPE correlate with pigmented fundus lesions (1d, arrows).

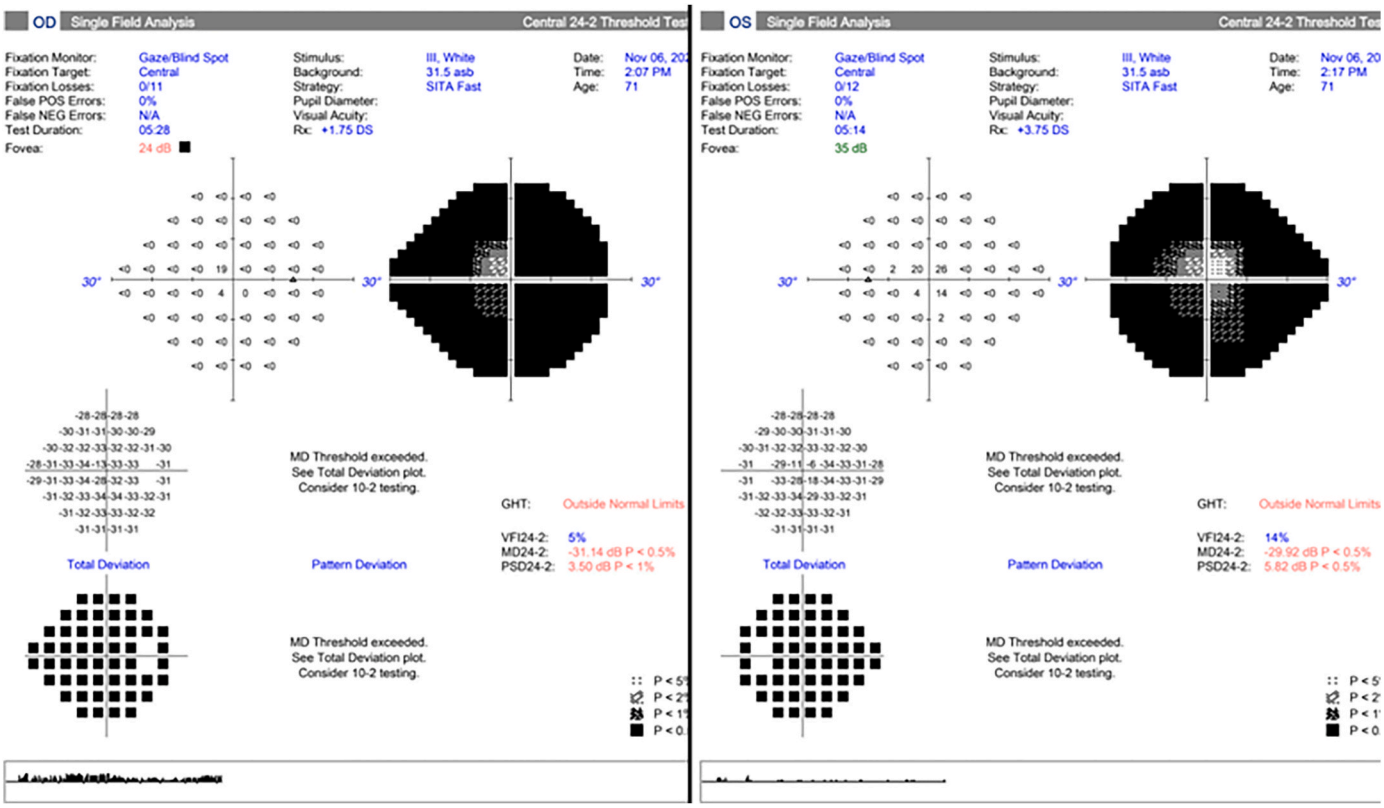

Fig. 2. Visual fields at presentation are remarkable for severe constriction in both eyes.

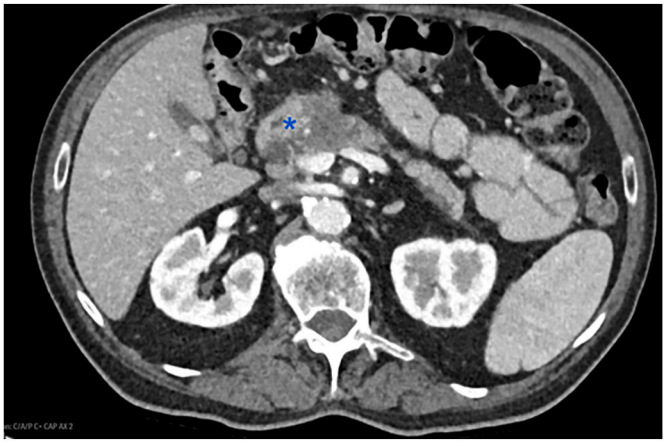

Fig. 3. MRI demonstrates spiculated mass at the pancreatic head which encases the superior mesenteric vein and abuts the superior mesenteric artery (asterisk). Local lymphadenopathy is present.

and RPE.[14,17] Lipofuscin in RPE originates in photoreceptor cell outer segments.[18] Increased lipofuscin formation by photoreceptor cells impaired by anti-PKM2 may have contributed to increased central FAF.[19] Anti-PKM2 induced RPE cell death may have resulted in more peripheral zones of reduced or absent FAF while punctate increased FAF, which has been attributed to RPE cell migration and clumping,[20] may indicate remaining viable albeit injured RPE.

According to the SEER database 2023, metastatic pancreatic cancer is a highly aggressive malignancy associated with a 5-year survival rate of less than 5%. Localized or regional disease has considerably better prognosis, highlighting the importance of early detection.[21] PKM2 has been linked to malignancies including pancreatic adenocarcinoma. Studies have suggested PKM2 is as effective as CA19-9 and CEA and potentially more specific for identifying pancreatic metastatic disease[22] and that PKM2 levels during the course of pancreatic cancer may correlate with disease activity.[23] Statistically significant associations between anti-retinal antibodies and specific malignancies have been reported.[24,25] Although anti-PKM2 was not among them, in patients with sudden unexplained visual loss, testing for anti-retinal antibodies including anti-PKM2 and systemic imaging is warranted and may be important in reaching a prompt, potentially life-extending diagnosis.

Anti-retinal antibodies participate simultaneously in functions both positive, as facilitators of an anti-tumor immune response, and negative, as promoters of retinal degeneration and visual loss. This creates a therapeutic dilemma in patients with paraneoplastic visual loss. PKM2 expression has been associated with survival[26] and this may suggest anti-PKM2 provides defense against tumor cell proliferation. Future investigation is warranted to determine whether initial systemic approach to visual symptoms, including treatment of the underlying malignancy, may be prudent before initiation of immune suppression or plasmapheresis. Alternatively, localized intraocular immune suppression may be warranted.

4. Conclusion

We present a case of confirmed p-AIR secondary to pancreatic adenocarcinoma with anti-PKM2 antibodies. This case illustrates anti-

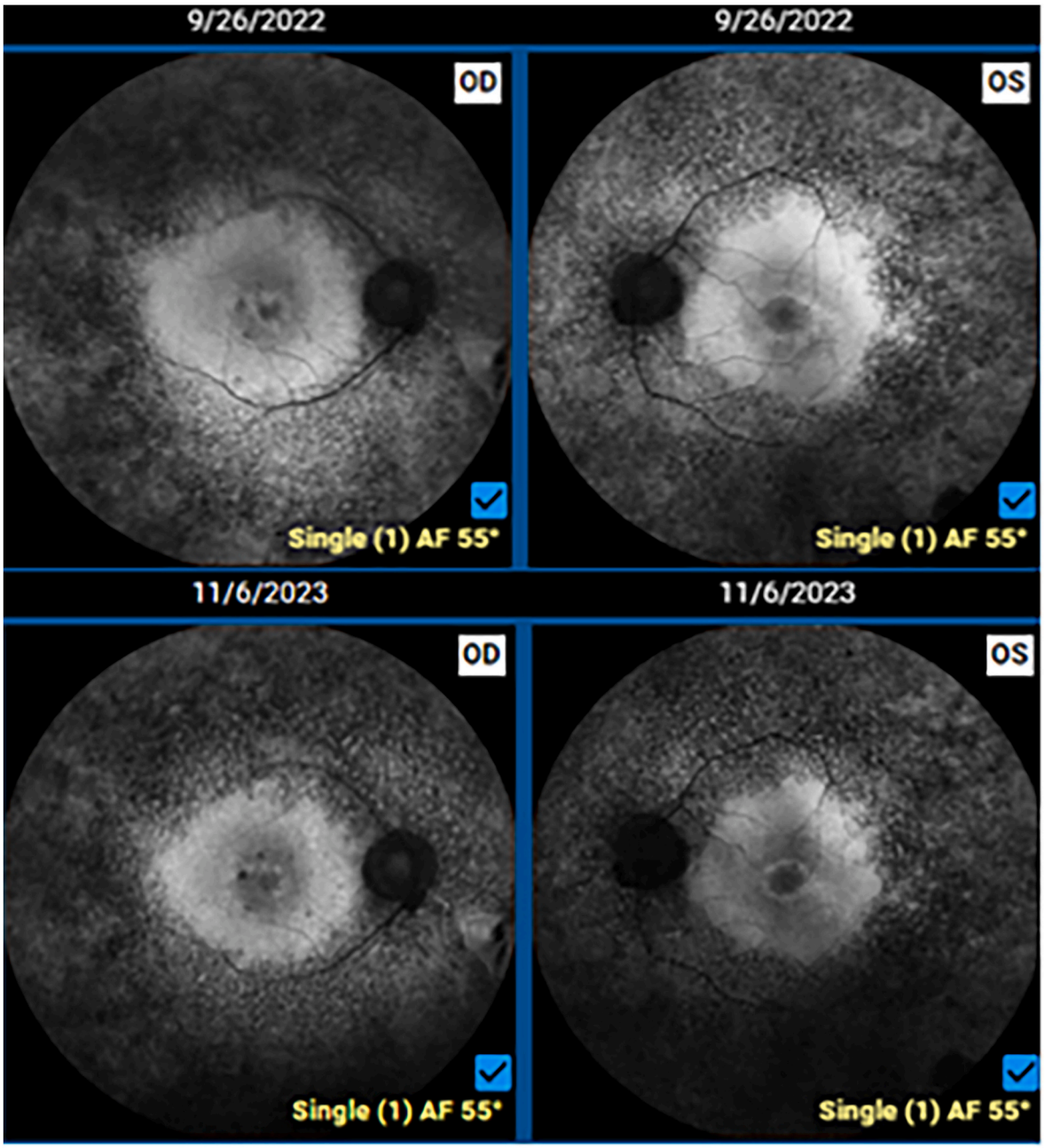

Fig. 4. Fundus autoflourescence at presentation (top) compared to 14 months later (bottom) demonstrates modest constriction and decrease in autoflourescence in both eyes.

PKM2 associated paraneoplastic retinopathy may be associated with occult pancreatic cancer and highlights the importance of systemic investigation for occult malignancy even when more common anti-retinal antibodies are absent.

5. Patient consent

Written consent to publish these cases has been obtained from the patient for the publication of this case report and accompanying images. This report does not contain any personal identifying information. The report adhered to the tenets of the Declaration of Helsinki.

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CRediT authorship contribution statement

Meredith P. Spitz: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **David R. Anderson:** Writing – original draft, Investigation, Data curation, Conceptualization. **Tamara R. Vrabec:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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References

1. Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF. Blindness caused by photoreceptor degeneration as a remote effect of cancer. *Am J Ophthalmol*. 1976;81 (5):606–613.
2. Jacobson DM, Thirkill CE, Tipping SJ. A clinical triad to diagnose paraneoplastic retinopathy. *Ann Neurol*. 1990;28:162–167.
3. Alexander KR, Fishman GA, Peachey NS, Marchese AL, Tso MOM. "On" response defect in paraneoplastic night blindness with cutaneous malignant melanoma. *Invest Ophthalmol Vis Sci*. 1992;33:477–483.
4. Gass JD, Gieser RG, Wilkinson CP, Beahm DE, Pautler SE. Bilateral diffuse uveal melanocytic proliferation in patients with occult carcinoma. *Arch Ophthalmol*. 1990; 108(4):527–533.
5. Weppelmann TA, Khalil S, Zafrullah N, Amir S, Margo CE. Ocular paraneoplastic syndromes: a critical review of diffuse uveal melanocytic proliferation and autoimmune retinopathy. *Cancer Control*. 2022;29, 10732748221144458. https://doi.org/10.1177/10732748221144458.
6. Ghadiri N, Yang Y, Burton BJ. Cancer-associated retinopathy in ampullary pancreatic cancer. *BMJ Case Rep*. 2019;12(11), e231444. https://doi.org/10.1136/bcr-2019-231444.
7. Li L, Zhang Y, Qiao J, Yang JJ, Liu Z. PKM2 in blood circulation facilitates tumor growth by promoting angiogenesis. *J Biol Chem*. 2014;289:25812–25821.
8. James AD, Richardson DA, Oh IW, et al. Cutting off the fuel supply to calcium pumps in pancreatic cancer cells: role of pyruvate kinase-M2 (PKM2). *Br J Cancer*. 2020; 122:266–278.
9. Rajala A, Wang Y, Brush RS, et al. Pyruvate kinase M2 regulates photoreceptor structure, function, and viability. *Cell Death Dis*. 2018 Feb 14;9(2):240. https://doi.org/10.1038/s41419-018-0296-4.
10. Lindsay KJ, Du J, Sloat SR, et al. Pyruvate kinase and aspartate-glutamate carrier distributions reveal key metabolic links between neurons and glia in retina. *Proc Natl Acad Sci USA*. 2014;111:15579–15584.
11. Gao J, Zhao Y, Li T, Gan X, Yu H. The role of PKM2 in the regulation of mitochondrial function: focus on mitochondrial metabolism, oxidative stress, dynamic, and apoptosis. PKM2 in mitochondrial function. *Oxid Med Cell Longev*. 2022 May 6;2022, 7702681. https://doi.org/10.1155/2022/7702681.
12. Sinha T, Naash MI, Al-Ubaidi MR. *The Symbiotic Relationship between the Neural Retina and Retinal Pigment Epithelium Is Supported by Utilizing Differential Metabolic Pathways*. vol. 23. 2020, 101004.
13. Lima LH, Greenberg JP, Greenstein VC, et al. Hyperautofluorescent ring in autoimmune retinopathy. *Retina*. 2012;32:1385–1394.
14. Robson AG, Michaelides M, Saihan Z, et al. Functional characteristics of patients with retinal dystrophy that manifest abnormal parafoveal annuli of high-density fundus autofluorescence; a review and update. *Doc Ophthalmol*. 2008;116:79–89.
15. Dysli C, Schuerch K, Escher P, Wolf S, Zinkernagel MS. Fundus autofluorescence lifetime patterns in retinitis pigmentosa. *Invest Ophth Vis Sci*. 2018;59:1769–1778.
16. O'Neal KD, Butnor KJ, Perkinson KR, Proia AD. Bilateral diffuse uveal melanocytic proliferation associated with pancreatic carcinoma: a case report and literature review of this paraneoplastic syndrome. *Surv Ophthalmol*. 2003;48:613–625.
17. von Rückmann A, Fitzke FW, Bird AC. Distribution of fundus autofluorescence with a scanning laser ophthalmoscope. *Br J Ophthalmol*. 1995;79:407–412.
18. Katz ML, Drea CM, Eldred GE, Hess HH, Robison Jr WG. Influence of early photoreceptor degeneration on lipofuscin in the retinal pigment epithelium. *Exp Eye Res*. 1986;43:561–573.
19. Sparrow JR, Yoon KD, Wu Y, Yamamoto K. Interpretations of fundus autofluorescence from studies of the bisretinoids of the retina. *Invest Ophthalmol Vis Sci*. 2010;51:4351–4357.
20. Sparrow JR, Gregory-Roberts E, Yamamoto K, et al. The bisretinoids of retinal pigment epithelium. *Prog Retin Eye Res*. 2012;31:121–135.
21. National Cancer Institute. *SEER Database Pancreatic Cancer Stat Facts*. National Institute of Health; 2023. https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed November 16, 2023.
22. Cerwenka H, Aigner R, Bacher H, et al. TUM2-PK (pyruvate kinase type tumor M2), CA19-9 and CEA in patients with benign, malignant and metastasizing pancreatic lesions. *Anticancer Res*. 1999;19:849–851.
23. Bandara IA, Baltatzis M, Sanyal S, Siriwardena AK. Evaluation of tumor M2-pyruvate kinase (Tumor M2-PK) as a biomarker for pancreatic cancer. *World J Surg Oncol*. 2018;16:56. https://doi.org/10.1186/s12957-018-1360-3.
24. Adamus G, Champaigne R, Yang S. Occurrence of major anti-retinal autoantibodies associated with paraneoplastic autoimmune retinopathy. *Clin Immunol*. 2020;210, 108317.
25. Adamus G. Autoantibody targets and their cancer relationship in the pathogenicity of paraneoplastic retinopathy. *Autoimmun Rev*. 2009;8:410–414.
26. Lockney NA, Zhang M, Lu Y, et al. Pyruvate kinase muscle isoenzyme 2 (PKM2) expression is associated with overall survival in pancreatic ductal adenocarcinoma. *J Gastrointest Cancer*. 2015;46:390–398.