Patient-specific Phase-Field modeling and simulation of Retinal Hemangioblastoma provides new perspectives on the role of anti-VEGF therapy

Franco Pradelli[1], Giovanni Minervini[1], Silvio C.E. Tosatto[1]

[1] DEPARTMENT OF BIOMEDICAL SCIENCES, UNIVERSITY OF PADOVA, VIALE G. COLOMBO 3, 35121, PADOVA, ITALY

Introduction

Retinal Hemangioblastoma (RH) is the most frequent and the earliest manifestation of the von Hippel-Lindau disease (VHL). It usually presents as a vascular and slowly growing tumor but can lead to life-threatening consequences. RH likely originates from the loss of heterozygosity in the VHL gene, which leads to angiogenic factors' (AFs) overexpression and abnormal proliferation. The effect of RH-driven angiogenesis (RHdA) could be recently observed in greater detail thanks to Optical Coherence Tomography Angiography (OCTA), which can detect the capillaries inside RHs much better than traditional fundus angiography. However, the absence of an animal model limits the study of RH Development (RHD) in time. Computational methods are rising as a valid alternative to study cancer dynamics, and, among all, Phase Field Models (PFMs) have proved remarkable results in reproducing tumor growth and angiogenesis.

Thus, we used PFMs to model and simulate RHD and RHdA. More precisely, we simulated the coupled effect of tumor growth, AFs overexpression, and angiogenesis, exploiting OCTA images from an actual patient's RH to validate our results.

Methods

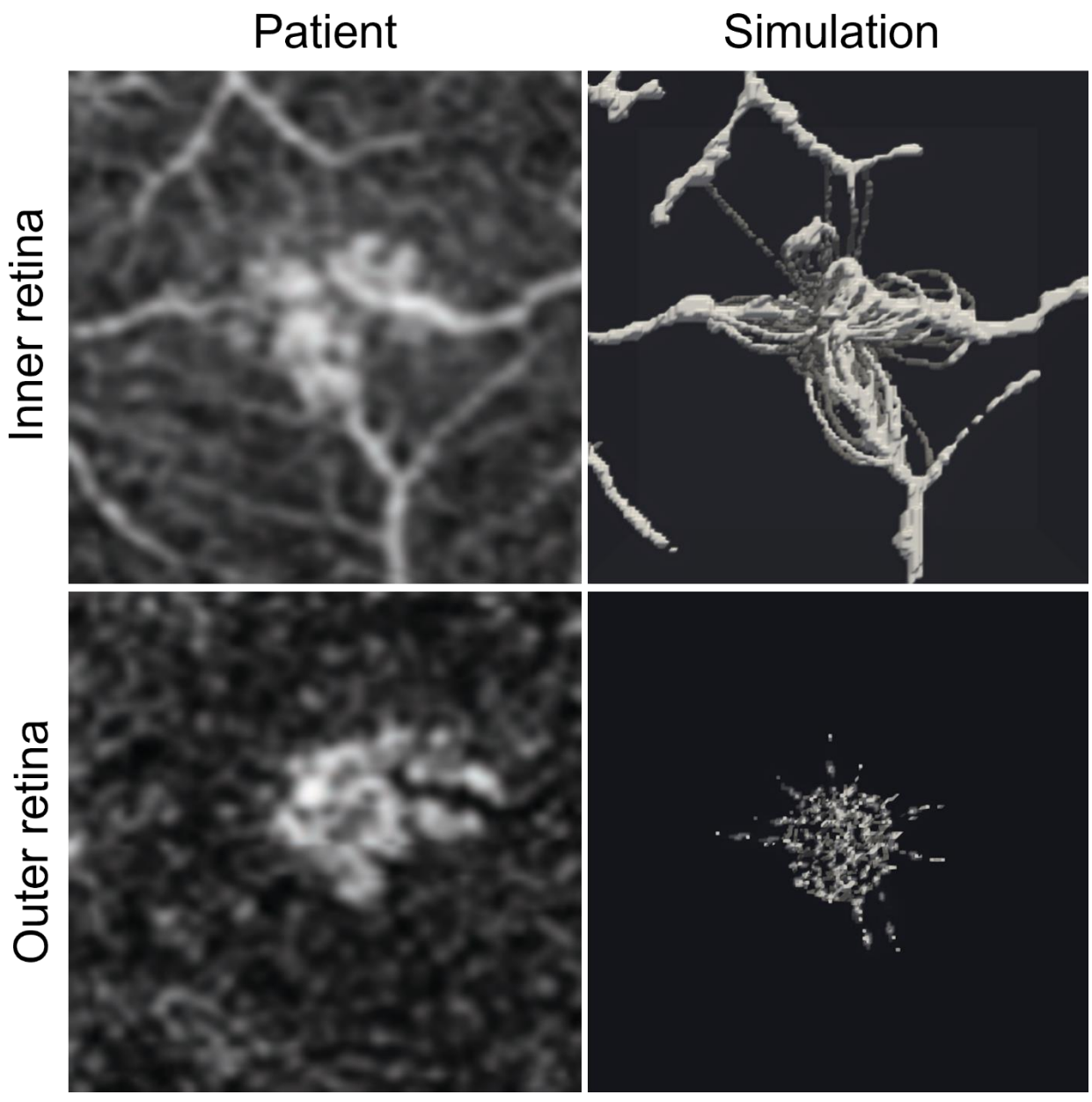
We selected the OCTA images from a recently published case report describing an early-stage RH. Given the extent of the RH, we could estimate the initial capillaries conformation and use that as the hypothetical initial condition. Then, we used our model to simulate RHdA and RHD, exploiting the FEniCS computational platform and our recently developed software, Mocafe. We estimated the model's parameters from experimental evidence reported in the literature. Finally, we validated our model using the patient's OCTA images.

Results

The simulations analysis is in progress, but our model seems able to reproduce the RH observed in the patient (Figure). Considering different credible values for the model's parameter, we could confirm that a slowly growing population of tumor cells overexpressing AFs is the simplest explanation for RHD. Our early observations further suggest that the RHdA might be sudden and rapid, leading to complete tumor perfusion in the order of days. The velocity of RHdA might explain the discouraging results of AF inhibition therapy for RH (e.g., anti-VEGF, anti-PDGF). Indeed, RH is usually diagnosed upon fundus examination, so when RH becomes visible, the RHdA might be already too advanced.

Discussion

To our knowledge, this is the first application of a mathematical model for studying RH. Our preliminary results align with the agreed RH pathology and experimental observations. These do not exclude other RH pathology possibilities but strengthen the mainstream theory. The simulated speed of RHdA is coherent with several studies on sprouting angiogenesis in vivo and in vitro and provides a new perspective on the applicability of AF inhibition therapy for RH. In conclusion, our work suggests that combining PFMs with OCTA provides a valuable tool for studying RH, partially filling the absence of an animal model.


Patient
Simulation
Inner retina
Outer retina