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Molecular diagnosis: Implications for ophthalmology

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ABSTRACT

The effort to subdivide diseases and to individualize therapies based on characteristics of the patient has been labeled precision medicine. Jameson and Longo define precision medicine as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" (Jameson and Longo, 2015). We illustrate how molecular diagnosis can be applied to orbital inflammatory disease to achieve the goals of precision medicine.

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1. Introduction

You are evaluating a 48 year old female with bilateral exophthalmos affecting her visual function for the last 6 months. Ten years ago she was treated for hyperthyroidism with radioactive iodine and she has been on thyroid supplementation since. She is now euthyroid. You take a thorough history and find that she is in excellent health except she has been having sinus "infections" regularly for the last two years. You decide to obtain laboratory tests. Thinking that this could be sarcoidosis, you obtain a chest x-ray and then a chest computerized tomography (CT) scan. Both show no abnormalities. Thinking that this could be a systemic vasculitis such as granulomatosis with polyangiitis (GPA) and sinus involvement, you obtain an anti-neutrophil cytoplasmic antibody (ANCA) study which is also negative. Then you order CT imaging of the orbits. The radiologist confirms the bilateral proptosis, thinks that the likelihood of either infection or primary or metastatic malignancy is low, but is unwilling to offer a more specific diagnosis as to the cause of inflammation. The radiologist judges that there is no extra-ocular muscle enlargement. Although the patient's disease is troubling, you decide that the severity does not currently require surgery to relieve pressure on the optic nerve. But you wonder if you should obtain an orbital biopsy, and if you do obtain this biopsy, what is the likelihood that the tissue will provide a specific diagnosis?

Although many clinicians approach the evaluation of orbital inflammatory disease differently, this scenario should be familiar to most ophthalmologists and to all orbital surgeons.

Establishing a precise diagnosis is the initial goal of most therapeutic encounters between a physician and a patient. Often that diagnosis is obvious from the history or the physical examination. In some instances, a serological test such as a fluorescent treponemal antibody titer plays a critical role in establishing the diagnosis. Sometimes imaging as with ultrasound, optical coherence tomography, or magnetic resonance plays a vital role. Within ophthalmology, current efforts are directed toward defining subsets of diseases such as diabetic retinopathy (Cunha-Vaz et al., 2014) and scleritis (Wakefield et al., 2013) such that more accurate prognosis and more tailored therapy can be offered. The last resort in differential diagnosis is often a biopsy so that tissue can be examined histologically. Although intra-ocular biopsies are uncommon, they can be invaluable in assessing some pathologies like lymphoma or melanoma. Biopsy of orbital tissue is a frequent approach to obtain a diagnosis of disease that causes a space-occupying lesion with the orbit.

In this review, we consider specifically the diagnostic value provided by biopsy of orbital tissue. We propose that the information gained from routine histology can be complemented and perhaps even exceeded by an analysis of the genes expressed in the removed tissue. We argue that molecular diagnosis, meaning an analysis of the genes expressed within a tissue, gives clues to pathogenesis, facilitates diagnosis, and might ultimately be fundamental in therapeutic decisions and assessment of prognosis. We use the term, transcriptomics, as a synonym for mRNA profiling since transcriptomics refers to an analysis of the RNA transcripts expressed in a tissue. The studies which we discuss represent an application of precision medicine to an assortment of orbital inflammations, some of which are frequently labeled as idiopathic or nonspecific. The approach that we describe requires refinements and validation before becoming a part of the routine approach to orbital disease. Thus, we offer both a review and a speculation about the future.

1.1. The differential diagnosis of orbital inflammatory disease

Orbital diseases can be divided into inflammations, infections, and malignancies. The inflammation can involve primarily extra-ocular muscle, orbital fat, the lacrimal gland, or some combination of these tissues. The most common inflammatory condition that affects the orbit is thyroid eye disease, also known as Graves' ophthalmopathy (Bartalena and Tanda, 2009). Graves' disease affects about 0.5% of the US and European population (Bartalena and Tanda, 2009). Seventy percent of patients with Graves' disease demonstrate extra-ocular muscle enlargement on imaging (Bahn, 2010). About 50% of patients with Graves' disease develop some symptoms of ophthalmopathy, although it is severe in only about ten percent of those affected (Bartalena and Tanda, 2009). Other non-malignant, non-contagious causes of orbital swelling include sarcoidosis (Rosenbaum et al., 2015b), GPA (Rosenbaum et al., 2015c) (previously known as Wegener's granulomatosis and also known as ANCA associated vasculitis), histiocytoses like Erdheim Chester disease (Hayden et al., 2007), and xanthogranulomas. A common diagnosis for orbital inflammation is nonspecific orbital inflammation (NSOI), which is also known as idiopathic orbital inflammation or orbital pseudotumor (Yuen and Ruin, 2003).

1.2. Molecular diagnosis as applied to cancer

One of the first applications of molecular diagnosis was reported by Louis Staudt and his colleagues in an analysis of lymphomas (Alizadeh et al., 2000). These cancers have distinct subsets clinically, but it is not always easy to distinguish the subset by routine light microscopy. For example, in a report in Nature in 2000, Staudt and colleagues analyzed gene expression in diffuse large B cell lymphoma (Alizadeh et al., 2000). They used gene expression profiling to show that some lymphomas, which could not be subdivided on the basis of routine light microscopy, resembled the pattern of expression of germinal center B cells and others resembled the pattern seen with activated peripheral blood B cells. Moreover, the prognosis was much better for the lymphomas with the germinal center pattern.

Similar technology has been employed in ophthalmology to identify two subsets of uveal melanoma (van Gils et al., 2008). The more common subset is unlikely to metastasize. But there are distinct gene transcripts associated with those melanomas that are most likely to involve the liver or other distant organs (van Gils et al., 2008). Estrogen receptor positivity is another example of a marker that distinguishes subsets, in this case subsets of breast cancer, but requires a technique other than routine histology for recognition (Yamamoto-Ibusuki et al., 2015).

1.3. Molecular diagnosis and inflammation

The most common application of molecular diagnosis is for malignancies, but inflammatory diseases are also yielding clues as a result of molecular diagnosis. For example, a subset of patients with systemic lupus erythematosus has up regulated genes in peripheral blood that are inducible by type I interferons (Baechler et al., 2003). This realization has led to clinical trials in which neutralization of interferon alpha is the target (Petri et al., 2013). Gene expression in CD8 T cells can aid in forecasting the prognosis in inflammatory bowel disease (Lee et al., 2011), systemic lupus erythematosus (McKinney et al., 2010), and GPA (McKinney et al., 2010). Synovitis has a broad differential diagnosis that includes rheumatoid arthritis, lupus, and spondyloarthritis. A pathologist has a limited ability to distinguish among these diagnoses, but transcriptomics can potentially provide a more precise differential (Yeremenko et al., 2013). Gene expression profiling has also been employed successfully to subdivide myocarditis (Lassner et al., 2014) and esophagitis (Wen et al., 2013).

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