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Title

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Permalink

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Journal

UC Merced Undergraduate Research Journal, 7(1)

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Publication Date

2014

DOI

10.5070/M471025001

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Undergraduate

The Misdiagnosis of the Doppelganger Diseases

Understanding Similarities in Disease and Treatment by Infliximab

By John Gemellos

Introduction

I. Where the Problem Lies: Misdiagnosis Today

Imagine you're a five year old; you have difficulty moving your limbs, and your eyes hurt whenever there is a bright light. You're told that you have juvenile arthritis and when you're older, you're told you have sarcoidosis as well. This goes on for years, as you're treated for these two illnesses all these years, yet nothing seems to be getting better. One day, you're told you've been misdiagnosed for almost 30 years, and only now will doctors start treating you for the real problem. For one patient this agonizing fantasy was a reality. Patients go misdiagnosed often because diseases present with primary symptoms that can be treated fairly easily, with the real problem lurking in the shadows until the medicine causes the disease to pounce on your well-being like a tiger. One such case occurs with two diseases that are different forms of each other: Early-Onset Sarcoidosis, and Blau Syndrome (which for future reference we will refer to as EOS

and BS respectively). Both of these genetic diseases are clinically indistinguishable from each other, and they get mistaken for “classic” Sarcoidosis, and juvenile arthritis, leading to a misdiagnosis of the real predator. However as it turns out, the issue with the misdiagnosis of EOS and BS has a new solution, as a prescription of a medicine called infliximab has led to a new treatment for the doppelganger diseases.

In order to understand these various diseases, it’s important to know where they come from and what they do. Sarcoidosis, according to MedicinePlus, is a disease that starts with little grain like lumps called granulomas appearing in the lungs, skin, and lymph nodes, as shown in Figure 1. Often these granulomas cause no problems, yet there are occurrences patients present with shortness of breath, fatigue, and constant coughs. The disease and symptoms are treated with Prednisone, in order to suppress your immune system and stop it from attacking itself and the rest of the body. Doctors prescribe prednisone and other medications like it to those with allergies to work in a similar fashion, otherwise the immune system is going to over work itself and start harming the body, instead of protecting it. However, while sarcoidosis can be a disease brought about by some other malady in the body or a reaction to some other microscopic invader, Early-Onset Sarcoidosis and Blau Syndrome have an entirely different cause.

II. Early-Onset Sarcoidosis and Blau Syndrome: Origins

Early-Onset Sarcoidosis and Blau Syndrome are two sides to the same coin. According to a series of articles by Dr. Nakano and Dr. Kambe published by Modern Rheumatism and Arthritis and Rheumatology, both diseases present with the same exact symptoms (which include skin rashes from granulomas and swelling of the joints and eyes, (otherwise known as arthritis and uveitis respectively), have a mutation on the same gene, and are clinically the same disease.

However, the microscopic difference between the twin diseases is in their mutations. EOS is the result of a type of mutation called a de novo mutation, which is a mutation that randomly occurs to the one of the parent's sex cells. This type of mutation cannot be accounted for or prevented, as it happens randomly. BS is an autosomal dominant mutation, meaning that it is passed down from parent to child. If the parent had BS, the child will most likely have it as well if they inherited the mutated gene. These two doppelganger diseases are essentially one in the same, meaning that they both erupt from the same problem.

Now with all of this talk about mutations, it is time to understand they are. While both mutations have different origins, the result is the same: they both end up being a nonsense mutation. Nonsense mutations replace a single nucleotide (a building block of DNA) with a different one altogether. Think of it like this: DNA is made up of specially chosen and specifically placed Lego bricks into an intricate pattern, but now one of the bricks is replaced with one that doesn't quite fit. This new Lego piece causes the cell to print out an incorrect protein, causing the whole structure to fall down, as illustrated in Figure 2. Both EOS and BS have their respective mutations on the same gene which codes for a specific protein that is important in fighting off certain bacteria. This new protein is unable to do its job, since the new Lego piece made the cell call for a different ingredient to make the protein, meaning that the protein is malformed, as seen in Figure 3. The mutated protein is what causes these diseases, since the immune system only recognizes what is native in the human body, and this mutated protein is considered foreign. The immune system then undergoes chain reactions or proteins that result in the inflammation seen in EOS and BS.

Infiximab: A New Approach to an Old Question

I. Case Studies and Infiximab Results

Patients with either EOS or BS are often misdiagnosed, since the symptoms are similar to “classic” Sarcoidosis, presenting with arthritis. These two doppelganger diseases in the end are mistaken for Sarcoidosis and juvenile arthritis when caught early on, since they present with granulomas and arthritis, leading to a misdiagnosis of the symptoms, but not the underlying problem. However, after analysis of the patient’s DNA, if mutations on the NOD2 gene are present, then the disorder is found discovered. What does this mean? It means that patients suffering from either of the twin disorders can undergo the correct treatment! This new treatment is rather recent however, and is still being studied, but the studies are all presenting with positive results.

According to Dr. La Torre et al., there appears to be positive results for patients with EOS or BS when treated with infiximab. The way this medicine works, according to the U.S. National Library of Medicine, is that it acts as an antagonist to the body’s TNF-alpha receptors. That must sound like gibberish, so here is what that means: infiximab will look like a certain protein, but when it is taken in by the receptors, it binds in such a way that the receptor can’t bind to the real deal. The end result is that infiximab inhibits the intake of the substance that causes the inflammation of the joints, eyes, and granulomas. This series of events is shown in Figure 4 below. Normally this medicine is prescribed to people with rheumatoid arthritis, ulcerative colitis, Crohn’s Disease, and other diseases that present with inflammation. Since infiximab was successful in treating diseases with inflammation, it’s amazing that it wasn’t considered to treat for EOS or BS.

II. Differentiating Diseases: Small Steps towards a Better Tomorrow

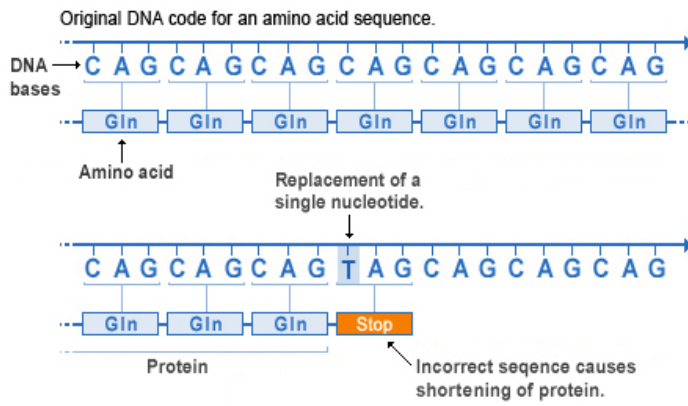
Dr. La Torre et al. began treating a patient who had gone 30 years misdiagnosed with juvenile arthritis and sarcoidosis with infliximab. In the article published by *Clinical Rheumatology*, the patient's true underlying illness was EOS, which was discovered after an analysis of her DNA showed a mutation on the specific gene. The medicine worked like magic, and the uveitis and arthritis decreased over time, as the doctors transitioned the patient from corticosteroid treatment to only the infliximab. After a follow up of 42 months, the patient seemed to have no negative side effects or any signs of relapse at all! And that's not all. Dr. Milman et al. have also had similar success in treating twins with EOS. In their article published by *AMPIS*, the twins were born with EOS, with symptoms starting at age 1, and worsening at 7. However, after infliximab treatment started, their symptoms seemed to disappear, and at age 20 (2-5 years after they started treatment), their quality of life had drastically improved, with no symptoms or hinderances from their illness. While this treatment seems to dramatically help those with EOS or BS, it doesn't seem to do much for those suffering from "classic" sarcoidosis, according to Dr. Judson et al.. In their article published by *Respiratory Medicine*, after completing a study with 122 patients suffering from sarcoidosis, the addition of infliximab did little to help or hinder their quality of life while on corticosteroid therapy. However, they did admit that a study that involved a corticosteroid withdrawal phase might give better results.

Figures



Figure 1: An example of Granulomas

Nonsense mutation



U.S. National Library of Medicine

Figure 2: An example of how nonsense mutations work

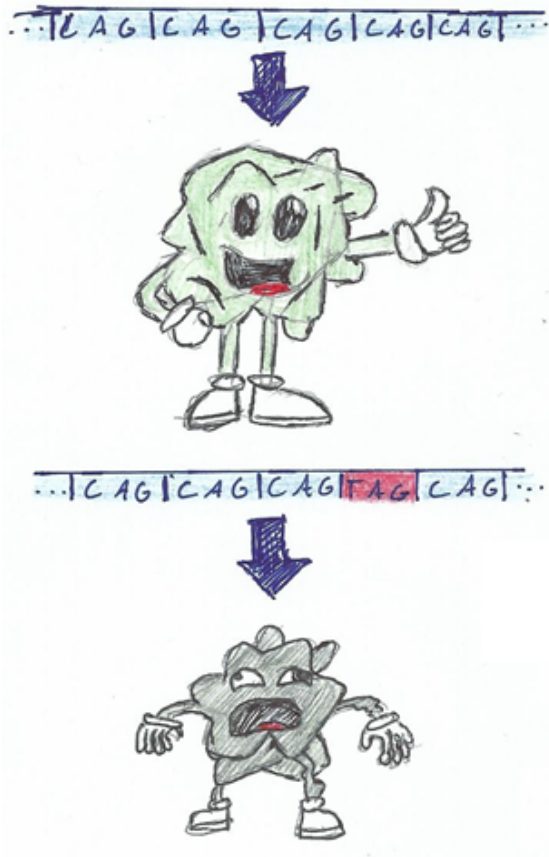


Figure 3: Cartoon representation of a healthy protein (top) and damaging mutation protein (bottom)

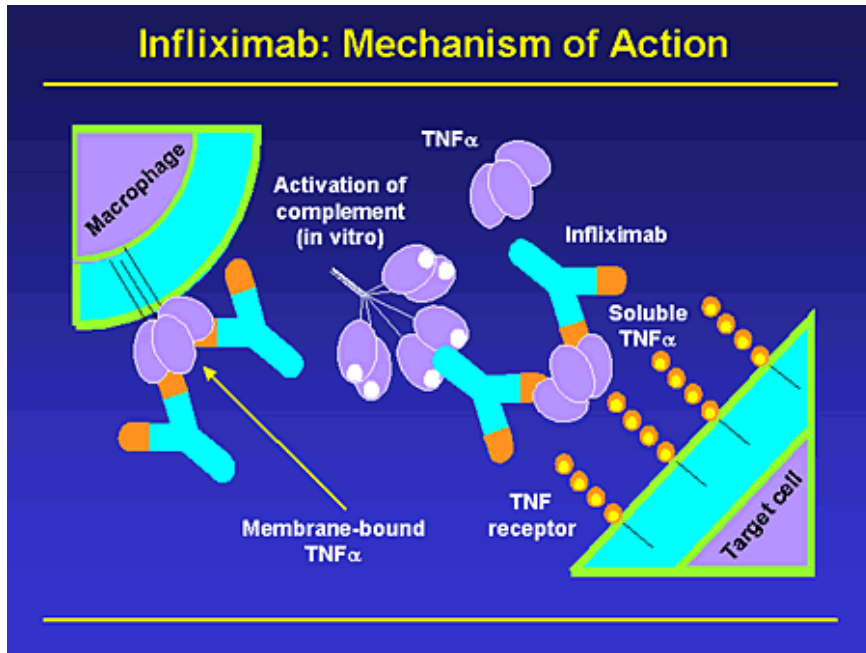


Figure 4: Representation of Infiximab mechanism of treatment

Conclusion

Misdiagnosis is a common problem amongst doctors, usually because the symptoms you see seem simple enough to treat with simple medicine. The underlying cause of the symptoms, however hides beneath the surface until it is time to strike. The misdiagnosis of EOS and BS occurred quite often, and only stopped recently since word of this misdiagnosis has spread. Now that doctors know to check the patients' DNA for the mutation, there is tremendously better chance of the patients suffering from EOS and BS being treated from an early age for the doppelgangers, as opposed to treated for a disease that isn't there. With studies like this spreading throughout the world, misdiagnosis is becoming less and less of a problem, improving the quality and restoring the balance of life.

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A Greek-American Major of Biological Sciences (emphasis in Microbiology and Immunology), Yiannis Gemellos spends the majority of his time studying. However, when he has the opportunity, he could be found playing his drum kit, skateboarding, or playing strategy games (such as Fire Emblem and Pokemon). He has various awards for Greek Folk Dancing, and prides himself in his culture. He is fluent in English, French, Greek and is currently learning Spanish. He also avidly listens to Punk music, Alternative music, and Indie Rock music, and has an interest in Operas (his favorite being Faust). He is also an involved member of Phi Delta Epsilon, a professional Greek organization for Medical and Pre-Medical students. He plans on one day attending medical school in hopes of becoming a doctor, specializing in infectious diseases. He is also easily identifiable by his extremely colorful skinny jeans.