

JAMES SCHALLER, MD DISCOVERS BABESIA AS A CANCER PRIMER

Are Various *Babesia* Species a Missed Cause for Hypereosinophilia? A Follow-up on the First Reported Case of Imatinib Mesylate for Idiopathic Hypereosinophilia

James L. Schaller, MD, MAR; Glenn A. Burkland, DMD; PJ Langhoff
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Background

When Drs. Schaller and Burkland were sent readers' responses to their 2001 MedGenMed article "Rapid and Complete Control of Idiopathic Hypereosinophilia With Imatinib Mesylate", they submitted the following reply as an update.

Abstract

Introduction: In 2001 we reported the first case of use of imatinib mesylate (Gleevec) for treatment of idiopathic hypereosinophilia syndrome (HES). These findings have been replicated in some patients with HES. After 1 year of taking imatinib, the patient stopped this medication, and during the last 5 years the patient has not experienced a relapse. He has, however, recently been diagnosed with babesiosis. This new diagnosis might relate to his HES.

Methods: After 6 years we decided to follow up on this patient's treatment. We interviewed the patient, his son, his aunt, and 2 consulting physicians and also reviewed relevant laboratory results to determine whether his HES had returned and whether his residual morbidity had changed.

Results: The patient has had no relapse of HES and his eosinophil counts have remained low-normal. He was recently diagnosed with babesiosis, and was prescribed atovaquone and azithromycin with a significant decrease in morbidity. His eosinophil cationic protein levels have also fallen to low-normal since starting atovaquone and azithromycin.

Discussion: New Babesia species are emerging as human infections. Most do not have available antibody or polymerase chain reaction diagnostic testing at this time. Manual differential examinations are of variable utility due to low numbers of infected red blood cells, suboptimal technique, and limited experience. Therefore, a diagnosis might need to be empirical at times, and should be based on signs and symptoms.

Conclusion: The patient has not relapsed in the 5 years that he has not been taking imatinib. Babesiosis should be added to the many possible causes of HES. It is unknown how often babesiosis causes HES as well as what percentage of HES patients have babesiosis.

Introduction

In 2001 we reported the first case of use of imatinib mesylate (Gleevec) for treatment of idiopathic hypereosinophilia syndrome (HES).[1] After 5 years, new information is available about the patient's care. Specifically, it is possible that an emerging complex protozoa infection, babesiosis, is associated with his medical history. On the basis of our experience with this patient, it appears that a diagnosis of babesiosis is not always simple. For example, the number of Babesia species that infect humans has grown from 4 to 10 or more during the last 15 years.[2] Available laboratory testing does not offer species-specific antibody and polymerase chain reaction (PCR) testing for these emerging species. Diagnostic clues for active Babesia, such as anemia, are not actually present in at least one aggressive emerging species (*B. duncani*)[3] (P.A. Conrad, oral communication, October 2006). Some Babesia experts caution that this intracellular parasite might be common.[4-6] As a background, the patient was diagnosed repeatedly with idiopathic HES, an often fatal illness that can damage a wide range of possible organs, including the heart, nervous system, lungs, liver, and kidneys. It is often treated with interferon-alpha and hydroxyurea, and we believe that these medications saved his life. For example, a small cerebral infarction related to his idiopathic HES did not recur over 6 years and his eosinophil counts were moderately controlled (eg, 12% eosinophils) on this combination treatment. However, his eosinophil cationic protein (ECP) was not controlled. (His values were 30-140 ng/mL with < 24 as the reference range.)

His interferon-alpha/hydroxyurea treatment increased or did not remove a profound intractable headache, severe fatigue, irritability, and concentration difficulties. After years on hydroxyurea and interferon-alpha, the severity of this morbidity or side effects motivated us to try a trial of imatinib mesylate. Treatment involved compounded capsules of 25 mg, used in doses between 75 and 100 mg per day, and was followed by an abrupt remission of HES

in a few weeks and a normalization of his ECP. He experienced no significant side effects. Over the course of a year, the patient's eosinophil count remained low-normal, and the patient decided on a trial of imatinib mesylate in 25-mg reductions over 3 months. He has not experienced a relapse during the past 5 years.

Since our initial publication, our findings have been repeatedly replicated.[7-13] In summary, these publications report many patients with HES have a dramatic positive response with imatinib treatment. Yet not all patients with HES respond to imatinib mesylate and not all retain positive responses. The cause of HES is unclear and heterogeneous. Causes for HES include dysregulation of interleukin 5, interleukin 3, and granulocyte-macrophage colony-stimulating factor. Of these cytokines, interleukin 5 appears to have the greatest role in the regulation of eosinophil maturation.[14] The positive effect of imatinib mesylate on HES has been attributed to many mechanisms. These include activated kinase such as Abl, platelet-derived growth factor receptor (PDGFR), KIT, and the novel fusion tyrosine kinase FIP1L1-PDGFRalpha, which is a consequence of an interstitial chromosomal deletion. All of these are inhibited by imatinib.[15] However, no single mechanism seems to explain all patients' positive response.[16]

Follow-up

Methods

After 6 years we decided to follow up on this patient's treatment. We interviewed the patient, his son, aunt, and 2 consulting physicians and also reviewed relevant sample laboratory results to determine whether his HES had returned and whether his residual morbidity while on imatinib had changed.

Results

After the patient was weaned off imatinib approximately 5 years ago, he had serial complete blood counts (CBCs), every 2-4 weeks for a year, due to a serious concern over a relapse. Eosinophils remained in the low-normal range, and ECP never surpassed the high-normal range.

Off imatinib, the patient was able to work a 50-hour week successfully, but did have ongoing medical and neuropsychiatric symptoms that began with the onset of his HES. The most significant was an intractable headache, paresthesia of the calves and feet, mild fatigue

(requiring 9 hours of sleep per night), mild irritability, mild cognitive rigidity, a mild decrease in interpersonal relational skills, mild depression, and middle-age onset of an obsessive personality disorder, according to a board-certified psychiatrist and neuropsychologist.

Although imatinib caused some transient relief from his severe headache, the benefit was lost and 2-week trials of 150 mg, 200 mg, 250 mg, and 300 mg did not regain any relief. The patient failed to receive headache relief despite full and complete trials with all major prophylactic and abortive medications over 12 years by 8 different neurologists. In 2006, a research-oriented, board-certified neurologist felt that the patient had failed all available headache medications. Other treatments for his remaining morbidities (eg, antidepressants from 5 medication classes and many mood stabilizers) had no clear benefit. In late 2006, the patient's son was slowly unable to function in school due to profound fatigue. Evaluations by specialists in endocrinology, infectious disease, oncology, and pediatric psychiatry yielded no clear diagnosis. Then the child was tested for Babesia by the family pediatrician after she read that Ixodes ticks can carry these protozoa. The family requested broad laboratory testing, and the results included a positive PCR for B microti. The pediatrician chose to ignore the negative IgG and IgM B microti titers and began an unspecified treatment for 3 weeks for presumed babesiosis infection; there was no clear benefit. The child is pursuing other medical consultations and is receiving home instruction due to ongoing profound fatigue and occasional sweats.

Also in late 2006, an aunt living in the same household began experiencing "signs of menopause" which she described as "waves of warmth, chills, and sweats." Her gynecologist, however, was not convinced on the basis of a menses history and laboratory results, and referred her back to her internist who thought her symptoms could just as easily be fever, chills, and sweats related to an infection. Her temperature was 99.0-99.8 °F during 2 weeks of daily afternoon checks. The aunt's internist heard about the patient's son and ordered B microti IgG, IgM, PCR, and sedimentation rate tests as well as manual CBC. After all returned negative, a relative who worked in pathology asked for the manual differential to be repeated. He called and discussed his limited experience and recent reading on Babesia with the pathologist, including the need for red blood cell (RBC) examination to be done at a power 1000x with oil, with instructions to look for specific Babesia intracellular RBC inclusions. The full recommendations to increase the capacity of the manual RBC examination are unavailable. Surprisingly, the repeat manual yielded a positive finding of a Babesia-like infectious agent in the woman's RBCs.

In this context, the same testing was run on our recovered HES patient, but no Babesia was found.

Over the following weeks, this academically advanced and motivated family began to discuss their experience with neighbors and others in their small community, an area characterized as having a very high deer population and also a presumed high Ixodes tick concentration. Some individuals reported having various Ixodes infections, including babesiosis. At this time, the aunt found an article on the WA-1 strain of Babesia on PubMed; it described 5 patients in a West Coast neighborhood as infected with a form never tested for in our HES recovered patient.[17]

The patient with HES in remission was then also tested for WA-1, newly named Babesia duncani,[3] which yielded negative results on IgM, IgG, and PCR. Our HES patient decided that Babesia should still be considered in his case. He did gardening and nature walking as hobbies, and believed that he was at higher risk than anyone in his household for Ixodes tick attachments. He reasoned with his doctors that his son had a positive PCR, had less outdoor contact than him, and that a repeated manual CBC only caught the aunt's Babesia after special communication with the pathologist.

Two consultants agreed on a 4-week babesiosis treatment trial to determine whether the patient's headache and other morbidity improved. He was placed on atovaquone (Mepron) 750 mg twice daily with fatty food to enhance absorption, and azithromycin (Zithromax) 250 mg 3 times daily. Babesiosis treatments may also be used to treat malaria; this makes some sense because Babesia and malaria are partially similar-appearing intracellular RBC parasites. The patient also treated himself with a derivative of Artemisia annua, a Chinese herb considered by the World Health Organization and the United Nations Children's Fund to be the first-line treatment for malaria if combined with a standard synthetic antimalarial agent.[18-25]

The patient has begun to improve with these treatments and therefore they are being extended a month. Specifically, the paresthesias of the calves and feet have markedly decreased and his fatigue has improved. His sleep has decreased from 9 hours a night to 7.5-8 hours a night. His mood has significantly improved and his cognitive rigidity, relational skills, and obsessive personality problems have improved approximately 75%. His ECP has gone from high-normal to low-normal levels. He has experienced a 50% overall improvement in his headache pain. He is not at baseline, but his mu agonist/antagonist pain treatment, a

buprenorphine/naloxone combination (Suboxone) which was the only treatment besides oxycodone to relieve his pain, was able to be reduced from 2 mg every 8 hours to a mere 1 mg per day. (Buprenorphine for pain is typically dosed at 3-4 times daily and rarely relieves pain at this low dose.)[26]

Currently, his physicians believe that his HES might have been due to an undiagnosed infectious agent, ie, Babesia. They feel that his residual morbidity is responding to babesiosis and malaria medications. Because the patient had been a gardener and nature walker for years before his HES, they believe that it is possible that he had Ixodes exposures via his brush- and woods-lined home and while hiking. Various family members, pets, and neighbors have had clear Ixodes tick attachments with rare highly variable rashes. The patient is not sure whether a few scalp "bumps" when grooming his hair were tick attachments.

Discussion

As of January 2007, many new species of Babesia have been identified and many have no specific human testing available in routine national laboratories.[2] The manual CBC used to identify Babesia and also a similar-appearing RBC parasite, malaria, is unreliable; malaria in allopathic centers is often missed, especially if the numbers of intracellular parasites are low.[27-29] The patient in this case had 2 close relatives in the same home with likely babesiosis diagnosed by some common symptoms and lab results. While treatments should not fully diagnose an illness, his positive response to 3 malaria medications used in babesiosis treatment is noteworthy.

Spontaneous unexplained remissions have been reported in HES patients with different treatments in the past, eg, interferon-alpha.[30] Because this patient has been free of HES lab findings for 5 years, we feel that he is probably outside the range of possible "cyclic eosinophil oscillations." [16]

Could interferon-alpha and imatinib control a Babesia-induced idiopathic HES? We do not know. However, low doses of natural human interferon alpha significantly inhibit the development of B microti infection in mice.[31]

Further, another partially related interferon, IFN-gamma, has antiparasitic benefits, including against Babesia.[32,33]

Imatinib has many mechanisms, and its ability to treat parasitic agents is not known. The tyrosine kinase system, however, is one target for the medication. Babesia contains a highly active protein kinase.[34] Viruses, bacteria, and parasites manipulate tyrosine kinase and related pathways of their hosts to achieve efficient entry, replication, and exit during their infectious cycles.[27]

Conclusion

The patient, the patient's physicians, and his family feel that Babesia is a possible cause for both his HES and other ongoing problems that have significantly remitted. We simply agree that it should be included in the differential diagnosis of HES before a diagnosis of HES is given; it is not on a list that is quite full and useful.[35] This emerging protozoa parasite should be considered in any idiopathic HES case because parasitic infections can cause hypereosinophilia. Yet many other causes of hypereosinophilia exist, eg, genetic abnormalities, atopy, hypersensitivity reactions, collagen vascular diseases, and tumors.

We have shown that our HES patient has not relapsed over 5 years after ending a successful trial of imatinib. Empirical treatment for babesiosis produced significant improvements in long-standing morbidity. Therefore, these specific emerging protozoa, Babesia, should be considered in HES patients, especially those with possibly common symptoms such as increased fatigue, fevers, chills, or sweats.[36,37]

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SCHALLER WORKS WITH FORMER JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION JOURNAL (JAMA) FEVERISHLY TO PUBLISH NEW FUNCTIONAL CANCER CURE OR SUGGESTS ACTUAL CANCER CURE IN SOME CANCERS

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Currently, his physicians believe that his HES might have been due to an undiagnosed infectious agent, ie, Babesia. They feel that his residual morbidity is responding to babesiosis and malaria medications. Because the patient had been a gardener and nature walker for years before his HES, they believe that it is possible that he had Ixodes exposures via his brush- and woods-lined home and while hiking. Various family members, pets, and neighbors have had clear Ixodes tick attachments with rare highly variable rashes. The patient is not sure whether a few scalp "bumps" when grooming his hair were tick attachments.

Discussion

As of January 2007, many new species of Babesia have been identified and many have no specific human testing available in routine national laboratories.[2] The manual CBC used to identify Babesia and also a similar-appearing RBC parasite, malaria, is unreliable; malaria in allopathic centers is often missed, especially if the numbers of intracellular parasites are low.[27-29] The patient in this case had 2 close relatives in the same home with likely babesiosis diagnosed by some common symptoms and lab results. While treatments should not fully diagnose an illness, his positive response to 3 malaria medications used in babesiosis treatment is noteworthy.

Spontaneous unexplained remissions have been reported in HES patients with different treatments in the past, eg, interferon-alpha.[30] Because this patient has been free of HES lab findings for 5 years, we feel that he is probably outside the range of possible "cyclic eosinophil oscillations." [16]

Could interferon-alpha and imatinib control a Babesia-induced idiopathic HES? We do not know. However, low doses of natural human interferon alpha significantly inhibit the development of B microti infection in mice.[31]

Further, another partially related interferon, IFN-gamma, has antiparasitic benefits, including against Babesia.[32,33]

Imatinib has many mechanisms, and its ability to treat parasitic agents is not known. The tyrosine kinase system, however, is one target for the medication. Babesia contains a highly active protein kinase.[34] Viruses, bacteria, and parasites manipulate tyrosine kinase and related pathways of their hosts to achieve efficient entry, replication, and exit during their infectious cycles.[27]

Conclusion

The patient, the patient's physicians, and his family feel that Babesia is a possible cause for both his HES and other ongoing problems that have significantly remitted. We simply agree that it should be included in the differential diagnosis of HES before a diagnosis of HES is given; it is not on a list that is quite full and useful.[35] This emerging protozoa parasite should be considered in any idiopathic HES case because parasitic infections can cause hypereosinophilia. Yet many other causes of hypereosinophilia exist, eg, genetic abnormalities, atopy, hypersensitivity reactions, collagen vascular diseases, and tumors.

We have shown that our HES patient has not relapsed over 5 years after ending a successful trial of imatinib. Empirical treatment for babesiosis produced significant improvements in long-standing morbidity. Therefore, these specific emerging protozoa, Babesia, should be considered in HES patients, especially those with possibly common symptoms such as increased fatigue, fevers, chills, or sweats.[36,37]

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