



Patient Report

An Important PJS History

A Report by
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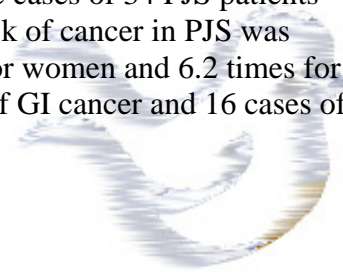
I've decided to send a long history of how PJS has been reported in the medical journals and textbooks. During the 20+ years I've been reading about PJS, I've seen the emphasis in reports and research shift again and again. As many have written to this list, physicians are working with outdated information. Because PJS is so rare, most physicians see few or no PJS patients. Then there's the fact that most of us move around, so few follow PJS patients for any length of time. Added to this is the problem that most of us see gastroenterologists, who specialize in the GI tract, possibly missing other manifestations of PJS including cancers and other tumors. Our physicians rely on the experts and the literature to determine how to treat us.

During the two years that this group has evolved, there've been some major re-visions of PJS among physicians, scientists and researchers. This history is my view of the highlights of those changes. Others would write it differently, but this seems like a good place to start.

The Medical Oddity Era

The original doctors who described PJS were interested in medical oddities and rare genetic disorders. Once it was determined that the syndrome consisted of hereditary spots and polyps, PJS quickly became the intellectual property (my term) of pediatricians, gastroenterologists and large medical institutions. Because PJS resembled FAP (Familial Adenomatous Polyposis), comparisons were drawn between the two syndromes. It soon became apparent that PJS polyps don't always lead to cancer, though FAP polyps do. Since the treatment for FAP polyps, which are located in the colon, is removal of the affected area, physicians in the early days tended to over treat PJS polyps by removing large sections of the small bowel, where they are located. This created long term problems like short bowel syndrome.

The early literature focussed on case reports, usually of medical oddities, and discussions of whether PJS leads to cancer or not and what the proper treatment of PJS patients is. One of the leading institutions, Mayo Clinic in Minnesota, followed a large group of PJS patients and determined that the cancer risk was very small. Unfortunately they focused on the malignant potential of polyps, rather than looking at the incidence of cancer in PJS. It wasn't until 1998 that Dr. Lisa Boardman reviewed the cases of 34 PJS patients seen at Mayo Clinic between 1945-1996, that an increased risk of cancer in PJS was found -- a relative risk of 18.5 times the general population for women and 6.2 times for men. There were 16 cases of cancer in 34 patients: 10 cases of GI cancer and 6 cases of extraintestinal cancer.



The Expanding Syndrome

In 1970, a pathologist named Dr. Scully and his group from Harvard described ovarian sex cord tumors and a rare type of cervical adenocarcinoma known as "adenoma malignum" and linked them both to Peutz-Jeghers syndrome. Dr. Scully is a respected pathologist who spent many years investigating these rare disorders by looking into a microscope, not into people's lives. His findings were published in Cancer Magazine, Gynecological Oncology and medical textbooks, so gastroenterologists didn't necessarily read them. And patient care didn't necessarily change.

The Cancer Era

Then in 1975, Dr. Utsunomiya from Japan did a follow-up study of 222 patients. There are many interesting things about this report including the abstract summary, "Among the 222 patients, cancer was histologically verified in 28. Fifteen early cancers occurred (3 gastric, 8 small intestine, 4 colon), and 11 advanced cancers (3 gastric, 1 small intestine, 6 colon and 1 both colon and small intestine). Mortality was lower than in patients with familial polyposis coli (FAP), but higher than the general population." But buried in the article itself is a table which is a follow-up of 102 cases, 36 of whom had died. "Of the deaths occurring before the age of 30, 42.9% were due to polyposis; death occurring after age 30 was attributed to neoplastic disease (cancer) in approximately 60% of the cases." Besides the GI cancers already mentioned there were one each liver, gall bladder, pancreas, uterus, ovary and bone and two lung. I recently learned from Dr. Iwama in Japan that in 1990 he reported on cancer in 20 PJS patients, 6 of whom had adenoma malignum of the uterine cervix. No other follow-up on PJS patients showed results similar to those of Utsunomiya, so most doctors didn't take PJS cancer risk seriously. The focus was still on malignant degeneration of PJS polyps and not on cancer risk.

In 1987 Dr. Giardiello of Johns Hopkins in Baltimore, Maryland, reported on 31 patients with PJS who were followed between 1973-1985. Cancer developed in 15 of the 31 patients (48 percent) - GI cancers in 4, non GI cancers in 10 and multiple myeloma in 1. The cancers were diagnosed when the patients were relatively young. Instead of arguing whether cancer arose in polyps, he analyzed the data and calculated a relative risk for cancer 18 times that of the general population.

Confirmation came from London in 1989. Dr. Spigelman from St. Mark's reviewed 72 PJS patients and found that malignant tumours developed in 16 (22%), of whom all but one had died. He didn't debate whether the cancers arose in polyps, but noted the ages and genders of the 9 patients with GI cancers and the 8 patients with non-GI cancers. He calculated the relative risk of cancer, 13 times the general population for GI cancer and 9 times the general population for all cancers and stated, "The chance of dying of cancer by the age of 57 was 48%."

The cancer era culminated in December of 2000 with Dr. Giardiello's meta-analysis of PJS patients that estimated a 93% risk of cancer in familial PJS. The analysis included six reports: Giardiello's prior report, Dr. Spigelman's report, Dr. Boardman's report, a report on the original Peutz family, another on the original Jeghers family and a report from New York on a family with 10 PJS folks. Though your physician may not have read the

meta-analysis that was printed in Gastroenterology, it has influenced the PJS experts and almost all newer articles quote it. Johns Hopkins published a guide for patients and families titled Peutz-Jeghers syndrome. Though a bit vague on actual cancer risk, the new surveillance recommendations are far more stringent than the old.

The Genetics Era

In 1997 the PJS gene was mapped to chromosome 19, the location is D19S886 on chromosome 19p13.3 to be exact. The gene is also referred to as STK11 and the gene product as LKB1. Scientists began testing PJS people and polyps and progressed to testing cancers (both in PJS & sporadic cases) for mutations in the PJS gene. An explosion in genetics and the mapping of the human genome led large hospitals and universities to develop cancer centers. Genetic counseling for people with hereditary predisposition to cancer like PJS is now common. PJS folks visit genetic counselors not only with family planning and genetic testing questions, but to discuss screening and long-term treatment plans.

Drug companies are interested in rare conditions, because they want to develop new drugs to treat common diseases like cancer. LKB1 is a tumor suppressor gene, by understanding its role in carcinogenesis, drug companies can develop drugs to target it or replace it. We aren't the market for these drugs, there just aren't enough of us, but we may benefit by drug company research some time. There is already a PJS drug trial underway in Finland, of Cox-2 inhibitors I think.

Rare disorders are important in the genetics era, because they allow models for study. There are many big players in PJS genetics. There are major researchers and groups investigating PJS in London (The Imperial Cancer Research Fund), Norway, Finland, Amsterdam, Germany, Japan, China, Italy and the US. Many authors collaborate with one another on different studies and articles. A typical study is the analysis of blood or tissue from PJS folks that looks for the mutation. Not all PJS patients have a chromosome 19 mutation and a second genetic location for PJS hasn't been found. I'd guess that research has been limited because there are few of us and many of us don't participate in research.

During this time, a steady stream of case reports flows through the literature. They come from all continents and tell all manner of stories. There are the usual stories -- we saw our first PJS patient and identified him/her by these signs and treated him/her in this way; our patient with PJS developed cancer and died or survived; our patient developed a rare manifestation of PJS and here's what we did. The sum of these reports is depressing and I seldom report them to the group, but I figure success stories are seldom printed. Imagine, saw a 50 year old patient with PJS for 3 year scopes and review, everything still fine.

A New Era - Molecular Biology and Proteomics

All this history is leading up to my next report. Researchers are now investigating the role of LKB1 and their findings should interest our physicians and us. My next report will go further into these new advances.

Hope this is understandable. I know that group members have entered the PJS timeline at different places and have different memories and impressions of "what the doctor ordered". Remember, most doctors look to the experts for how to treat people with rare conditions. As the advice changes, our care changes. What was good care in the 1960s or 1980s is bad care now. By watching these trends and eras, we can forecast good care for the 21st century.

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