Leśniowski-Crohn disease – historical overview

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For ages there have been reports in medical literature of acute or chronic, bloody or mucous diarrhea, with accompanying fever, weakness and loss of body weight.

Diagnosis based on histopathological and microbiological assessment of tissue specimens was possible only after introduction of routine autopsies in hospitals in 18th-19th century (1). Previously autopsies were performed only in exceptional cases, most commonly in the event of death of some noble born. In 1643, autopsy performed in Louis XIII who died at the age of 42, demonstrated numerous ulcerations of the small and large intestinal mucosa as well as an abscess and perirectal fistula. For 16 years Louis XIII was suffering for periodic recurrences of bloody diarrhea, abdominal pain, fever and arthritis. Pathologists at this time reported his case as tuberculous inflammation of ileocecal intestinal fragment or segmental inflammation of this fragment of unknown etiology (2).

In 1612 Wilhelm Fabry was performing an autopsy of a boy who had died for persistent diarrhea with abdominal pain located in the right subcostal region and found a narrowing in a cecum that was intussuscepted to the ileum and made free intestinal passage impossible. When the preparation was cut, the wall of the cecum was found to be ulcerated and fibrotic (3).

In 1761 G.B. Morgagni from Forli in his paper „De Sedibus et Causis Morborum” described an ulceration and perforation of inflamed distal ileum with perforation and enlargement of mesenteric lymph nodes in a 20-year old patient who died of diarrhea with fever that had persisted for 2 weeks (3, 4).

Multiple similar cases were reported at the beginning of 19th century.

In 1813 C. Combe and H. Saunders observed ulcerations in the large intestine and distal ileum as well as a 3-feet stricture in a patient with a history of diarrhea and abdominal pain (3).

In 1828 Abercrombie presented intestinal diseases in his book and classified them as acute or chronic, symptomatic mucosal ulcerations, pediatric intestinal inflammation and intestinal disease accompanying other disease; furthermore he classified them as affecting ileum, large intestine or only the rectum (1).

In 1830 Abraham Colles from Dublin described terminal ileitis in children as well as fistulas: perianal, rectovaginal and rectovesical (3).

Reports by J.C.W. Lever (5), Bristowe (6) and J. Cruveilher in his book „Pathological Anatomy” (1) may also correspond to inflammation of the ileocecal region.

In 1859 Samuel Wilks from London performed an autopsy of a 42-year old woman – Mrs. Bankes, who had been a wife of a doctor-bigamist, suspected of poisoning her. She had a history of diarrhea and fever that had persisted for several months. Autopsy demonstrated ulceration of the mucosa of the whole large intestine as well as inflammatory changes in the terminal portion of the ileum (over the distance of three feet from the Bauchin’s valve). This supported the conclusion that the
patient’s death was caused by an acute, non-infectious diarrhea as a result of the above mentioned lesions (1, 7). This was one of three cases in which inflammatory changes occurred both in the large and small intestine, out of three thousand autopsies performed by Wilks. This case was reported as a simple ulcerative colitis. However, a century later it was found to be Crohn’s disease (1). In 1859, in the first edition of “Lecture”, Wilks presented a classification of intestinal inflammatory lesions. In the second edition, he extended this classification, adding inflammation of the ileum that affected the whole thickness of the wall. Eventually, benefiting from the progress of microscopic technology, he reported granulomas (“pyoid corpuscles”) in the intestinal wall. Microscopic examinations also demonstrated that the strictures within the ileocecal valve result from a chronic inflammatory process rather than tuberculous or neoplastic changes (1).

In 1889 Samuel Fenwick from London, found adhesions between small intestine loops and a fistula between the cecum and the small intestine during an autopsy of a 27-year old woman who died of persistent diarrhea with loss of body weight. Distal fragment of the ileum was enlarged and hypertrophied while the ileocecal valve was stenosed. In the same year, Fenwick devoted his whole lecture to non-neoplastic stenoses of the ileocecal valve, although did not present any histopathological findings (3).

Between 1850 – 1899, Fielding reported 31 cases of enteritis in Transactions of the Pathological Society of London: 4 had small intestine disease, 15 large bowel involvement, and 12 had both small bowel and colon affected. He reported also 29 similar cases in Dublin, starting from 1840 (1).

Polish surgeon, Antoni Leśniowski (fig. 1), in his paper titled „Przyczynki do chirurgii kiszek” (Treatise on the surgery of the bowels), which was an account of his lecture given in Warsaw Medical Society on April 21, 1903, reported a case of a female patient hospitalized in Baby Jesus Hospital in Warsaw (fig. 2) that could correspond to “terminal ileitis” (8, 9).

We quote the author: „on 27 December 1899, a 30-year old female patient (J.R.) was transferred from department of internal medicine to department of surgery, due to abdominal mass. The patient was deaf-mute, she could not write. Therefore, communication with the patient regarding origin and development of the disease was extremely difficult. Communication using sign language indicated that had been sick for approximately one year, she had experienced episodes of flatulence and abdominal pain, in particular after meals, and that these complaints had recently significantly exacerbated and had been accompanied by vomiting. She had her bowel movements everyday, they had normal appearance. Percussion of the right half of her abdomen did not
reveal any abnormality. However, on the left side there is a resistance at the site of the above mentioned protuberance, to the top reaching a finger above the umbilicus, to the bottom two fingers below the umbilicus, as a band of such width heading upwards and to the left of the umbilicus. Palpation demonstrated an extremely painful mass that could not be precisely palpated due to painfulness, sausage-like, hard, very mobile, in particular in its top portion. On January 3, 1900, due to the above mentioned painfulness of the mass, the patient was examined under chloroform anesthesia. Then we found that the mass which had a size of a large man’s fist, had a sausage-like shape, was unusually mobile in every direction and could especially easily be shoved under the liver. However, it was not a right kidney because the latter could be palpated in its normal location. To the bottom the mass reached as far as the entrance of the pelvis minor so that the bottom fragment of the mass could be palpated through the front fornix of the vagina. When the patient was anesthetized, we irrigated her colon with water and the irrigation produced a band that crossed the abdomen from the left to the right, at the level of the umbilicus. From the latter the resistance headed obliquely upwards, reaching the liver and finally to the right iliac fossa. When the intestines were forcefully filled with water, the mass resolved completely. When water was evacuated from the colon so that the intestine tension became smaller, the mass could be palpated on the right side of the abdomen, under the liver; during further evacuation of water, the mass transferred lower and lower, approaching umbilicus and becoming more mobile. The above specified data obtained from imprecise interviews and possibly detailed examination of the patient led to the conclusion that the abdominal mass that led to the patient’s hospitalization in the department of surgery, caused chronic stenosis of the colon. It could be assumed, with high certainty, that it was located in the colon, namely in the hepatic flexure. With regard to the tumor nature, we had the right to believe that it was not tuberculosis of the large intestine, its hypertrophic form, since this form was usually located in the cecum. We were less sure if it was a malignancy. Nevertheless, in view of lack of detailed interview data, we had to be content with such incomplete diagnosis. All in all, a surgery was required and this position was presented to the patient. The patient refused to undergo surgery and on day 5 she left the hospital. However, two weeks later she was admitted to the hospital again. During this time her general health significantly deteriorated. She suffered from persistent diarrhea, pain attacks, nausea and occasionally vomiting. In view of her general health, major surgery seemed to be contraindicated. I performed the surgery on 24 February 1900, under careful chloroform anesthesia. I took the cut through the midline, starting 4 cm above the umbilicus and ending 6 cm below it. The peritoneum was pale, slightly thickened. My hand, introduced to the peritoneal cavity, encounted a mass at the level of the umbilicus and easily extracted it outside. Indeed it was located in the hepatic flexure of the colon and was extensively ingrown into the thickened, folded omentum. Along with adhesions, it had a size of a large fist, was elongated and had a highly uneven surface. Hard lymph nodes could be palpated in the mesentery of the large intestine: they had size of a bean to small cherry, were numerous immediately adjacent to the intestine, more scarce near the spine. The omentum was gradually ligated and cut off from the mass. Thereafter I typically resected an affected segment of the intestine, 2 to 3 cm from both sides of the mass. I cut a wedge from the mesentery, attempting to remove any lymph node that could be palpated, due to unknown nature of the operated mass. A wall of highly dilated proximal part of the intestine was hard, highly thickened and very fragile. I anastomosed ends of the intestine with a three-floor suture and a wound in the abdominal wall with a one-floor suture. I filled the peritoneal cavity with 1000 cm$^3$ of warm physiological solution of kitchen salt before tying the last suture. The course of surgical procedure was successful. The patient’s condition slowly but steadily improved; one month after the surgery she left her bed while after 5 weeks she was discharged from the hospital, feeling very well, completely free from her previous complaints.

Leśniowski described pathological changes in this case. We quote: “Length of the removed large intestine was 21 cm the intestinal wall was highly thickened, reaching 3 cm. The whole intestinal mucosa was reddened, very plumpy, folded. Multiple papillary and polypous lesions could be seen on the folds. Holes in
the mucosa were seen between the folds. A probe can enter small cavities through these holes. The probe can penetrate, from these cavities, under the mucosal membrane in any direction, sometimes as far as 3 cm and go out through a second hole in the mucosa. The muscular membrane is highly hypertrophied, swollen. The subserous connective tissue is hypertrophied; thickened, hardened omentum extensively adhered to the serous membrane. Soft foci, filled with granuloma and odorous lysis can be found occasionally in the highly hypertrophic subserous tissue with scarry degeneration; from these foci the probe goes, through more or less tortuous turns, throughout the wall to these holes between mucosal folds. We were surprised because at the site of the mass we did not found neither tissue that could be malignant nor even a serious ulceration. We suspected that it could be some chronic inflammation of the intestinal wall, namely so called follicular dysentery (8).

The subsequent, number 22 of weekly “Medycyna” states. Clinically, acute dysentery results first in prolonged, persistent, debilitating diarrhea, pain attacks, and when the lytic process approaches peritoneal surface, peritonitis becomes irritated. However when intestinal lumen becomes progressively stenotic, symptoms of chronic intestinal stenosis appear at first. Our case, as the above provided macroscopic description indicates, was indeed a case of such mass that resulted from chronic follicular dysentery. However I do think that this type of masses in not an extremely rare event: I rather think that in some cases, that were not studied in detail, they were mistaken for colon malignancy. Unfortunately, so far we have not enough data to be able to differentiate in detail respective intestinal masses. With regard to masses resulting from chronic follicular dysentery, the key element is a recent history of bloody diarrhea, immediately preceding the current complaint. Because our patient was unable to inform us about her dysentery (due to her disability), while we precisely located the mass, we were unable to guess its proper nature” (9).

In 1913 T. Kennedy Dalziel from Glasgow provided a correct description of pathomorphological changes in terminal ileitis basing on examination of 13 patients, preceding Crohn’s report by almost 20 years. First of the patients described by Dalziel, had been suffering from diarrhea and spasmodic abdominal pain since 1091 and thereafter died of intestinal obstruction. Dalziel found inflammation of the whole small intestine and enlarged mesenteric lymph nodes during an autopsy. Dalziel associated this ileitis with bovine mycobacterial ileitis, called John’s disease (3).

Until 1930 American doctors reported cases of inflammation of intestinal wall of hyperplastic nature with granulomatous lesions, initially called hyperplastic intestinal tuberculosis. In 1922 – 1937 J.J. Pemberton and P.W. Brown reported 39 such cases. Clinical symptoms were similar to that described previously since these changes occurred in children, adolescents and young adults who sometimes were operated for suspected appendicitis. Patients often reported a history of fever, spasmodic abdominal pain, diarrhea and loss of body weight. Pathological lesions involved the terminal segment of the ileum or ileocecal segment (3, 5).

In 1925 Coffen from Portland reported a case of 20-year old patient who underwent three segmental resections of the small intestine over 13 months due to recurrent symptoms of intestinal obstruction (1). Terminal ileitis was found to occur more often in Jews, especially in Ashkenazi Jews, in some countries (i.e. United States, Sweden, England), while not in other countries (Denmark or Norway) (3).

F.J. Nuboer from the Netherlands in 1932, M. Golob from New York in 1932 and A.D. Bissell from Chicago in 1934 reported cases of similar disease, immediately preceding its description by Crohn and associates (fig. 3).
As early as in 1870-1880 doctors from Mount Sinai Hospital in New York noted that inflammation of the terminal segment of ileum and cecum, with course similar to tuberculous ileitis but without Mycobacterium tuberculosis in postoperative material is common in the Jewish population (1, 3). These observations were performed mainly by surgeons: A. A. Berg and his assistant Leon Ginzburg as well as a surgeon-pathologist Gordon Oppenheimer. Ginzburg assisted Berg for several years in resections of terminal segment of the small intestine which was affected by inflammatory process. These observations resulted in a paper titled: "Non-Specific Granuloma of the Gastrointestinal Tract" reporting on sixteen patients. Soon after it was written, a patient came to Doctor Winkelstein’s office; he was suffering from bloody diarrhea that reportedly was caused by hemorrhoids. However, to support diagnosis, the doctor suggested that gastrointestinal examinations should be performed: sigmoidoscopy and barium enema. The patient did not agree to undergo these examinations and visited Doctor Crohn’s office. Doctor Crohn diagnosed intestinal tuberculosis and advised the patient to go to Florida to use sunbathing. During this treatment the patient experienced an episode of intestinal obstruction. He was operated by Doctor Berg in Mount Sinai Hospital. Dr. Berg performed ileocecal resection. When Doctor Crohn found out that his patient had been operated, he was very eager to see the postoperative specimen. At this time Doctor Winkelstein was a volunteer at Department of Pathomorphology of Mount Sinai Hospital and he personally showed the specimen to Doctor Crohn. Doctor Crohn asked what the disease was and was answered that this was called “terminal ileitis”. Crohn said that he never heard of such disease before. Doctor Winkelstein explained that Doctor Ginzburg and Oppenheimer reported sixteen such cases, courtesy of Doctor Berg, and they claimed that these were inflammatory changes in the intestinal wall. This was neither tuberculosis nor malignancy. When several weeks later another patient visited Doctor Crohn, this time the doctor diagnosed him with “terminal ileitis”. Then Crohn came to talk with Berg and said that he was interested in this disease. Berg ordered Ginburg and Oppenheimer to hand over the test results to Crohn. However they resisted and even a special hospital committee that was appointed to examine this case, ruled that the first report of this disease should be by the younger doctors. However the committee decided that this controversy should be settled by the involved parties to prevent scandal. Doctor Berg again ordered his employees to hand over the test results to Crohn and threatened to fire them should they do otherwise. On 11 December 1931 Crohn wrote to American Society of Gastroenterologists that he had discovered a new bowel disease – “terminal ileitis” and would like to share his views (1).

On 2-3 May 1932 Ginzburg and Oppenheimer presented a study on “terminal ileitis” at session of American Society of Gastroenterologists in Atlantic City and published it, along with Crohn’s name, in Overview of American Society of Gastroenterologists in the same year. Its expanded version was published in Annals of Surgery in 1933 (1, 10).

On 13 May 1932 at the session of Gastroenterological and Proctological Section of American Medical Association in New Orleans, Crohn personally presented results of “his team’s” investigation including fifteen patients. Inflammatory changes were restricted to the terminal segment of the ileum (8-12 inches). Diarrhea was the cardinal clinical symptom of this chronic disease. Another pathognomonic sign was a tendency toward fistula formation, usually between small and large intestine but occasionally fistulas with orifice on an anterior abdominal wall. All reported patients had undergone a surgical procedure involving resection of the affected bowel segment. Two patients died of peritonitis. Etiological factor was unknown but according to Crohn this disease had neither malignant nor bacterial etiology and could be caused by disturbances of mesenteric blood flow (1, 10).

Thereafter these results were published on 15 October 1932 in JAMA, in a paper titled “Regional Ileitis- A Pathological and Clinical Entity”. An initial title of the paper “Terminal ileitis” was changed following a suggestion of its reviewer, J. Arnold Burger, who claimed that the term “terminal” was associated with agonal “ileitis” rather than distal. Doctor Berg was asked both by Crohn and his assistant to be the first author of this paper but refused to do so as well as refused to be a co-author of this paper since he did not contribute to this
paper. Furthermore Berg ordered to insert names of the authors in alphabetical order. Thus, after publication in JAMA, this disease was termed “Crohn’s disease” in international literature (1, 8, 10).

However in Polish medical literature “ileitis terminalis granulomatosa” is called “Leśniowski-Crohn disease” to commemorate description of this disorder by Antoni Leśniowski in 1904 (8).

In 1933 Harris et al. reported inflammatory changes of the large intestine and ileum (3). A year later Colp mentioned a possibility of large intestine involvement in Crohn’s disease (6) and in 1936 B.B. Crohn and B.D. Rosenak described 9 cases of ileitis together with right sided colitis (3, 6). For the first time the term “Crohn’s colitis” was used by Wells in 1952 (6).

In 1983 a paper by C.L. White et al. was published in Gut. The authors reported a case of a 29-year old female suffering from both Crohn’s disease and ulcerative colitis. 11 years after resection of distal ileum and colon up to the level of ascending colon for Crohn’s disease, this patient developed left sided ulcerative colitis (11).

In 1938 R.J. Coffey emphasized characteristic features of this disease: subacute or chronic course, tendency to stenosis of intestinal lumen and fistula formation. In 1943 Tallroth coined a term ileitis allergica (allergic ileitis) for terminal ileitis due to large number of eosinophils present in the inflammatory infiltration in the intestinal wall (3, 5).

Later investigations focused on epidemiology and etiology of terminal ileitis.

In 1960 E.D. Acheson analyzed data from 2320 males who were diagnosed with, among others, regional ileitis and concluded that it most commonly occurred in Jewish population. In 1960’s A.I. Mendeloff et al. from Baltimore claimed that nonspecific inflammatory bowel diseases occur both in men and women, were more common in Caucasians than in other races, occurred in Western countries, most commonly in the Northern Europe, predominantly in Jews from North America and Europe, in residents of cities, less common rural areas and these disorders had an inherited component. In 1982 J.M. Rhodes et al. from Cardiff, Wales, published results of a letter-based survey that indicated that almost half of patients with Crohn’s disease were cigarette smokers (3, 5).

Effect of stress as a triggering agent was investigated by e.g. Blackburn in 1939 and Grace et al who were surprised by their observations indicating that stress in a large degree could contribute to occurrence of first disease symptoms or another episode of the disease. Other researchers, such as Crockett and Ardali, focused on the fact that this chronic, severe disease led to emotional disturbances, depression, etc. (3).

The reported possible etiological factors of this disease include Mycobacteriaceae (Kanssaii, paratuberculosis) and Mycobacterium Linda, anaerobes (Eubacteria strains Me46, Me47, Bacteroides vulgatus, coprococcus, bifidobacteria, Campylobacter fetus ssp. jejuni, Yersinia enterocolica, Chlamydia trachomatis as well as bacterial constituents (lipopolysaccharides, peptidoglycaines, oligopeptides), metabolic products (toxins and neurotoxins) and virions and prions (3, 12). However neither of the above mentioned pathogens has been considered an etiological factor of Leśniowski-Crohn’s disease. Similar situation applies to viruses that were tested as possible etiological factors of this disease, i.e. Epstein-Barr, CMV, Echo, Cocksockie A and B, adenovirus, rotavirus and Norwalk virus. The most probable etiological factor is measles virus although this is still a controversial issue. Bovine infection caused by Mycobacterium paratuberculosis, so called Johne’s disease (1913) induces similar pathologic lesions in the intestinal wall as are found in Leśniowski-Crohn’s disease. The former can also affect terminal segment of the ileum. Infection causes also inflammation of this intestinal segment in guinea-pig, enterocolitis in Cocker spaniel dogs (1954) and granulomatous colitis in Boxer dogs. However neither of these bowel inflammatory diseases has histological features of Leśniowski-Crohn’s disease (3, 12).

Researchers focused their investigations also on the effect of immune factors on development of nonspecific inflammatory bowel disease. Kirsner and Palmer in 1954 noticed that these diseases involve disturbances of immune system in the intestinal mucosa as a result of its hypersensitivity to nutrients, pollen and other allergens. Studies by Kirsner et al., Broberg et al. and Bernier et al., have proven that patients with ulcerative colitis have antibodies in their blood that react with...
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In 1960's, investigations of intestinal antigens, antibodies against intestinal mucosa and experimental immune-mediated colitis flourished. However, due to imperfect nature of technology and methods, effect of the above mentioned factors on development of nonspecific inflammatory bowel disease has not been proven.

Currently, over 50 years later, investigations of immunology of nonspecific inflammatory bowel disease are much more extensive and they result in new models of therapy.

REFERENCES


COMMENTARY

On 19 October 1887, at the session of Medical Society of Cracow chaired by doc. P. Pieniżek, prof. A. Obaliński presented an exceptional case operated by himself. Summary of this presentation was published by Przegląd Lekarski (Volume XXVI, No. 46, page 626). It was related to (quote): a 30-or-so year old woman who has been suffering for chronic constipation for several years; at the beginning of August the author had to proceed to laparotomy due to potentiation of her complaints, probably in the course of intestinal stenosis. After opening the abdominal cavity, significantly distended small intestine loops were found and a mass (quote): in the cecal region (displaced to the middle and slightly to the left), which had a size of two fists, uneven surface, nodular, hard, with its posterior wall adhered and numerous adjacent enlarged glands. Obaliński thought that it was an inoperable malignant tumor, created (quote): an artificial rectum, by suturing a 15-cm fragment of iliac intestine above the mass in the abdominal wound. After the surgery and after bowel emptying through the fistula, within a few weeks natural stools appeared and the fistula closed spontaneously. Furthermore, a large mass that was palpated through the abdominal wall, almost complete-

1 Przemysław Pieniżek (1950-1916) was the first professor of laryngology in Poland. He obtained Veniam legendi from laryngology and rhinology on JU in 1879. He was a chairman of Medical Society of Kraków twice.
2 Prof. Alfred Obaliński (1843-1897) was the head of department of surgery of St. Lazarus Hospital in Cracow.
ly resolved so that (quote): cancerous nature of this mass was put in serious doubt and we suspected an atypical form of chronic cecal inflammation.

The discussion after Obaliński’s presentation included, among others, Ludwig Rydygier, who (quote): claims that Lauenstein\(^3\) has already emphasized that there are masses of inflammatory etiology that are mistaken for malignancies and he agrees that the mass reported by Obaliński must have been of inflammatory nature.

Avoiding discussion whether this could be some form of Crohn’s disease, I present it here to prove that intestinal masses of inflammatory etiology had been known to Polish surgeons several years before Leśniowski published his own observations on this issue. Not derogating from achievements of such outstanding surgeon as prof. Antoni Leśniowski, we must ask a question: whether a disease should be associated with a name of the subject who was the first to publish a possible case or the one who reported it, proving that this was a previously unknown, newly found disease unit?

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\(^3\) Carl Lauenstein (1850-1915) was a “Oberarzt der Chirurgischen Abteilung des Diakonissenspital Bethseda” then.