Case Reports in Gastroenterology

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955

Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

Gastric Juvenile Polyposis with High-Grade Dysplasia in Pachydermoperiostosis

L. de Mestier[a] S. Moreau[b] C. Neuzillet[a] P. Ruszniewski[a]
Y. Panis[c] P. Hammel[a]

[a]Service de Gastroentérologie-Pancréatologie, Pôle des Maladies de l'Appareil Digestif, Hôpital Beaujon (AP-HP, Université Denis Diderot, Paris VII), [b]Service d'Anatomie et Cytologie Pathologique, Hôpital Beaujon (AP-HP), and [c]Service de Chirurgie Colorectale, Pôle des Maladies de l'Appareil Digestif, Hôpital Beaujon (AP-HP), Clichy, France

Key Words
Pachydermoperiostosis · Stomach · Juvenile polyposis · Dysplasia · 15-Hydroxyprostaglandin dehydrogenase

Abstract
Pachydermoperiostosis (PDP) is the primary form of hypertrophic osteoarthropathy. It is a very rare disease consisting of pachydermia, digital clubbing and radiologic periostosis. Various digestive symptoms in PDP are seen in 11–49% of patients and juvenile polyps may be found at gastric endoscopy. We report here the history of a patient with PDP who was referred for assessment of severe anemia. Endoscopy of the upper digestive tract showed multiple polyps of the stomach with two huge lesions exhibiting foci of high-grade dysplasia. This observation suggests that PDP can be considered as a precancerous condition of the stomach and systematic screening using endoscopy should be considered in these patients.

Introduction

Pachydermoperiostosis (PDP), or Touraine-Solente-Golé syndrome, is the primary form of hypertrophic osteoarthropathy [1]. It must be distinguished from the secondary form of hypertrophic osteoarthropathy which is much more frequent (95%) and mostly due to various cardiac diseases, and pulmonary or thyroid malignancies. PDP has a dominant autosomal transmission with variable expression and penetrance. PDP is due to mutations of the gene encoding for 15-hydroxyprostaglandin dehydrogenase (15HPGD) [2, 3]. A familial history is found in 25–38% of patients. PDP predominates in males (sex

Prof. Pascal Hammel
Service de Gastroentérologie-Pancréatologie, Pôle des Maladies de l'Appareil Digestif
Hôpital Beaujon, 100 boulevard Leclerc, FR–92110 Clichy (France)
E-Mail pascal.hammel@bjn.aphp.fr

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955
Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

ratio 9:1). Consanguinity seems to be a major risk factor. The typical form of the disease includes pachydermia, digital clubbing and radiologic periostosis. About one third of patients affected with PDP have upper digestive symptoms [1]. Clinical manifestations of PDP are thought to be due to excessive collagen formation and dysregulation of matrix proteins due to fibroblastic hyperactivation [4]. We report here the observation of a patient with PDP who presented symptoms of severe digestive bleeding due to juvenile polyposis of the stomach that contained foci of severe dysplasia.

Case Report

A 33-year-old Caucasian man was admitted to the emergency room for melena and deep asthenia. Hemogram showed severe microcytic anemia (hemoglobin 26 g/l, mean corpuscular volume 63 fl). Clinical examination was normal except for objective signs of anemia. There was no abdominal pain. His past history only showed a known PDP, with progressive thickening of the hands, feet and scalp, associated with digital clubbing (**fig. 1**). Radiological aspect was typical with diffuse periostosis. There was no history of smoking or alcohol intoxication. There was no familial history, particularly no PDP or digestive disease.

Multiple polypoid lesions were seen in the stomach on upper gastrointestinal endoscopic examination. Two of them measured 8 × 6 cm and 6 × 5 cm, respectively. Histological examination of the biopsy specimens from several polyps showed hyperplastic crypts, with cystic dilatations in an edematous stroma with inflammatory infiltrates. Foci of high-grade intraepithelial neoplasia were found in two large polyps. There was neither sign of *Helicobacter pylori* infection nor of lymphocytic gastritis. Endoscopic ultrasonography of the stomach showed important homogeneous thickening of the gastric mucosa. Colonoscopy and videoenteroscopy were normal.

After a multidisciplinary discussion we decided to perform gastrectomy, because of the severe anemia, the young age and good condition of the patient, and finally the extension of lesions together with foci of high-grade dysplasia. Surgery consisted in total gastrectomy with systematic D1 lymphadenectomy. There was no postoperative complication and the patient was discharged 8 days later.

Macroscopical examination of the resected stomach showed the presence of multiple polyps, most of them being located in the antrum (**fig. 2**). Histological examination showed features of juvenile polyps. These were characterized by elongated, tortuous and dilated foveolar and glandular epithelium. The lamina propria was abundant, edematous and infiltrated with plasma cells and lymphocytes. Foci of high-grade dysplasia were present in the two huge polyps (**fig. 3**a, b). We proposed the diagnosis of juvenile polyposis of the stomach with foci of high-grade dysplasia. The patient remained asymptomatic after a 9-month follow-up without recurrence of anemia.

Discussion

PDP is a very rare disease. The complete form includes pachydermia, digital clubbing and radiologic periostosis. Seborrhea, hyperhydrosis, acne, cutis verticis gyrata, gynecomastia, joint pain and flushes are minor criteria [1]. In our patient, the diagnosis of PDP was made based on pachydermia, cutis verticis gyrata and digital clubbing, associated with typical radiological diffuse periostosis.

Upper digestive symptoms are reported by 11–49% of patients with PDP [5–7]. At endoscopic examination, gastroduodenal ulcers, atrophic gastritis, hypertrophic gastropathy, Menetrier's disease, juvenile polyps or gastric adenocarcinoma can be found (**table 1**). Finally, combination with Crohn's disease or exudative enteropathy have also been reported [5, 7, 8]. Jajic and al. [9] reported 76 cases of PDP: in 21 patients, upper

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955
Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

gastrointestinal endoscopic examination was performed that showed gastroduodenal ulcers in 13 and hypertrophic gastropathy in 8 patients. Finally, involvement of the upper digestive tract in PDP may be underestimated as most patients are asymptomatic and thus do not undergo endoscopic examination. Since PDP is often associated with gastric changes and occasionally with gastric premalignant lesions, an endoscopic follow-up seems to be important in patients affected with PDP who complain of upper digestive symptoms [10]. In our patient, the uncommonly severe anemia (hemoglobin 26 g/l) was probably due to a chronic silent bleeding, explaining the surprising good clinical tolerance. Due to the microcytic character of the anemia, a potential role of myelofibrosis, a condition seen in PDP, seemed to be unlikely.

Association of PDP with juvenile polyposis of the stomach has been reported in only one patient before [10]. Jass et al. [11] established a working definition of juvenile polyposis: ≥5 juvenile polyps of the colorectum and/or juvenile polyps throughout the gastrointestinal tract and/or any number of juvenile polyps with a family history of juvenile polyposis. The colon is systematically affected (98%), but polyps are less frequent in the stomach (14%) or the small bowel (9%). In the stomach, polyps are mostly located in the antrum and dysplasia occurs in nearly 30% of cases. Adenoma and adenocarcinoma may be found [11–13]. Systematic endoscopic screening is recommended in the follow-up of these patients [13]. Patients affected by juvenile gastric polyposis often undergo gastrectomy because a malignant course is possible. In our observation, PDP combined with juvenile polyposis was circumscribed to the stomach as colonoscopy and videoenteroscopy were normal. Since foci of high-grade dysplasia were found in the huge polyps, we considered reasonable to perform total gastrectomy to preclude a malignant course.

Few authors have related hypertrophic osteoarthropathy associated with gastrointestinal polyposis [14–16]. Osteoarthropathy seemed to be secondary to polyposis and was often associated with cystic fibrosis of the liver or the lungs and/or arteriovenous pulmonary malformation. In our observation, these abnormalities were not found. Thus, osteoarthropathy was not likely to be secondary to gastric neoplasia, since the latter developed several years after the diagnosis of PDP.

The physiopathology of PDP remains misunderstood. Mutations of the gene encoding for 15HPGD are involved [3, 4], leading to an increase in the plasmatic rate of prostaglandin E2 (PGE2). A chronic increase of PGE2 seems to be implicated in periostosis by stimulating osteoblastic growth, and also in pachydermia and clubbing by stimulating fibroblastic growth. Pathogenic implication of vascular endothelial growth factor has been suggested by the hypertrophy of the endothelium on skin biopsies [2]. These chronic vascular changes may lead to deregulation of the anabolic activity of fibroblasts, resulting in unorganized accumulation of collagen in the matrix, responsible for pachydermia and digital clubbing. As PDP may be due to fibroblastic hyperactivation and hypercollagenosis of the extracellular matrix, these mechanisms may be responsible for chronic hypertrophic gastritis, which is often associated with this disease.

Whether PDP is a precancerous condition is ill-defined. Staalman and Umans [17] have reported the combination of PDP with malignant lymphomas or melanomas. 15HPGD is a tumor suppressor gene which counterbalances the production of PGE2 by cyclooxygenase 2 in gastric, colorectal, breast and lung cancers [18]. The oncogenic process seems to be associated with an early increase of cyclooxygenase 2 expression and

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955
Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

so PGE2, then an abolition of 15HPGD expression as a second step. Moreover, 15HPGD may be an antitumoral agent as it leads to the inhibition of tumor invasion and cellular migration [19].

Conclusion

Involvement of the upper digestive tract seems to be frequent in PDP, even though it has not been systematically explored. Upper gastrointestinal endoscopic examination should be part of the check-up in patients affected by this disease. In case of severe gastric involvement, it seems cautious to propose a periodical endoscopic follow-up. Surgical gastrectomy should be considered in symptomatic patients or in those whose biopsies reveal severe dysplasia to preclude a malignant course.

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955
Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

Table 1. Clinical, endoscopic and pathologic characteristics of gastric affection in several patients with PDP

First author and year of publication	Patients	Digestive symptoms	Upper gastrointestinal endoscopic examination	Pathology
Current observation	1	Digestive bleeding Chronic anemia	Gastric polyposis	Juvenile polyposis Foci of high-grade dysplasia
Lam, 1983 [20]	2	Abdominal pain	Gastroduodenal ulcers Hypertrophic gastritis	Hypertrophic gastritis (Menetrier's disease)
	2	Abdominal pain	Gastroduodenal ulcers Atrophic gastritis	NS
Tanaka, 1991 [21]	1	Chronic anemia	Gastroduodenal ulcers Duodenal diverticula	NS
Matsui, 1991 [6]	8	Abdominal pain	Hypertrophic gastritis	Hypertrophic gastritis
	5	Abdominal pain	Gastroduodenal ulcers	NS
Jajic, 1992 [7]	10	Abdominal pain	Gastroduodenal ulcer	NS
	14	Abdominal pain	Atrophic gastritis	Atrophic gastritis
	1	Pyrosis	Peptic esophagitis	Peptic esophagitis
Pignone, 1992 [22]	4	Abdominal pain	Gastroduodenal ulcers	NS
	3	Abdominal pain	Hypertrophic gastritis	Hypertrophic gastritis
	1	Abdominal pain	Normal	Atrophic gastritis
Cooper, 1992 [23]	1	Abdominal pain	Gastroduodenal ulcers	NS
Seung-Chul, 1998 [24]	2	Abdominal pain	Gastroduodenal ulcers	NS
Jajic, 2001 [9]	13	Abdominal pain	Gastroduodenal ulcers	NS
	8	Abdominal pain	Hypertrophic gastritis	Hypertrophic gastritis
Lakshmi, 2001 [25]	1	Abdominal pain	Hypertrophic gastritis	Hypertrophic gastritis (Menetrier's disease)
Ikeda, 2004 [10]	1	Chronic anemia Abdominal pain	Gastroduodenal ulcers Gastric polyposis Peptic esophagitis	Juvenile polyps Gastric cancer
Sethuraman, 2006 [8]	2	Abdominal pain	Lymphangiectasias	Exudative enteropathy
Okten, 2007 [26]	1	Abdominal pain Chronic anemia	Hypertrophic gastritis	Hypertrophic gastritis
Rodríguez, 2009 [27]	1	Chronic anemia	Hypertrophic gastritis	Hypertrophic gastritis

NS = Data not shown.

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955
Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

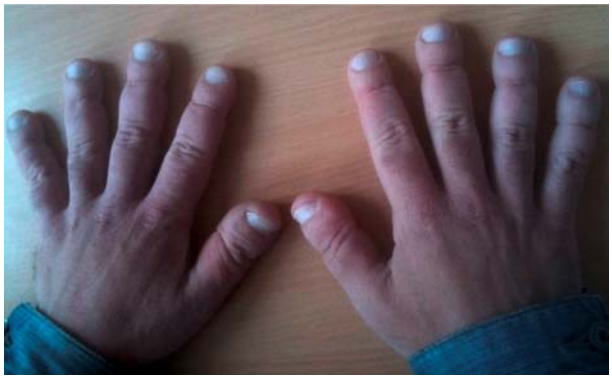

Fig. 1. Photograph of the hands showing diffuse thickening and digital clubbing.

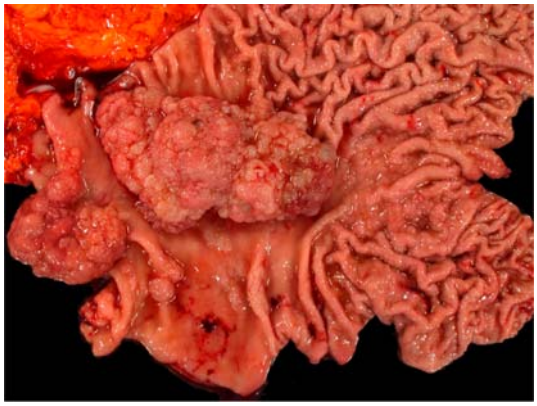

Fig. 2. Macroscopic pathologic examination of the resection specimen showing numerous polyps with papillary surface in the gastric angulus and antrum.

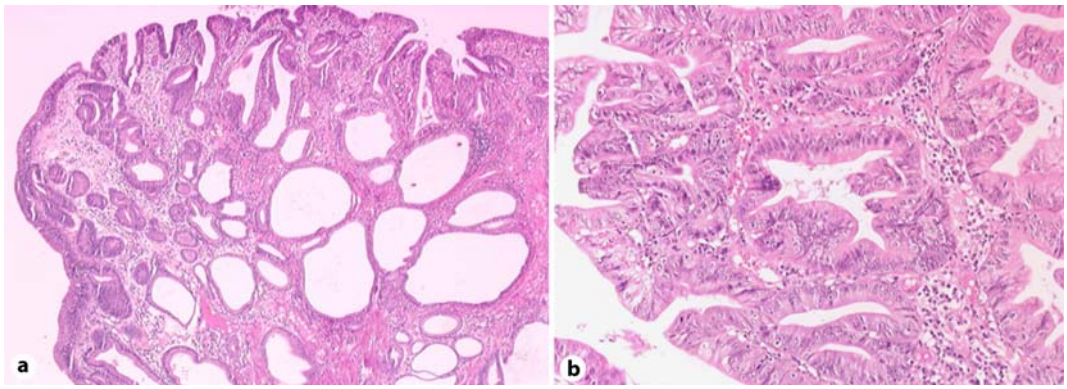

Fig. 3. **a** Histopathology of the resected polypoid lesion (HE, ×25) showed elongated, tortuous and dilated foveolar crypts with inflammation in the lamina propria. **b** Histopathology of the resected polypoid lesion (HE, ×200) showed high-grade intraepithelial neoplasia in a small area of a huge polyp.

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955
Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

References

1 Auger M, Stavrianeas N: Pachydermoperiostosis. Orphanet Encyclopedia 2004. http://www.orpha.net/data/patho/GB/uk-pachydermoperiostosis.pdf.

2 Uppal S, Diggle CP, Carr IM, et al: Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat Genet 2008;40:789–793.

3 Yüksel-Konuk B, Sirmaci A, Ayten GE, et al: Homozygous mutations in the 15-hydroxyprostaglandin dehydrogenase gene in patients with primary hypertrophic osteoarthropathy. Rheumatol Int 2009;30:39–43.

4 Martinez-Lavin M, Vargas A, Rivera-Viñas M: Hypertrophic osteoarthropathy: a palindrome with a pathogenic connotation. Curr Opin Rheumatol 2008;20:88–91.

5 Castori M, Sinibaldi L, Mingarelli R, Lachman RS, Rimoin DL, Dallapiccola B: Pachydermoperiostosis: an update. Clin Genet 2005;68:477–486.

6 Matsui Y, Nishii Y, Maeda M, Okada N, Yoshikawa K: Pachydermoperiostosis, report of a case and review of 121 Japanese cases. Nippon Hifuka Gakkai Zasshi 1991;101:461–467.

7 Jajic I, Jajic Z: The spectrum of skeletal and visceral abnormalities in 52 patients with primary hypertrophic osteoarthropathy. Clin Exp Rheum 1992;10:73.

8 Sethuraman G, Malhotra A, Khaitan B, Sharma V, Kumar R, Makharia G: Familial pachydermoperiostosis in association with protein-losing enteropathy. Clin Exp Dermatol 2006;31:531–534.

9 Jajic Z, Jajic I, Nemcic T: Primary hypertrophic osteoarthropathy: clinical, radiologic, and scintigraphic characteristics. Arch Med Res 2001;32:136–142.

10 Ikeda F, Okada H, Mizuno M, et al: Pachydermoperiostosis associated with juvenile polyps of the stomach and gastric adenocarcinoma. J Gastroenterol 2004;39:370–374.

11 Jass JR, Williams CB, Bussey HJR, Morson BC: Juvenile polyposis: a precancerous condition. Histopathology 1988;13:619–630.

12 Hizawa K, Iida M, Yao T, Aoyagi K, Fujishima M: Juvenile polyposis of the stomach: clinicopathological features and its malignant potential. J Clin Pathol 1997;50:771–774.

13 Covarrubias DJ, Huprich JE: Best cases from the AFIP. Juvenile polyposis of the stomach. Armed Forces Institute of Pathology. Radiographics 2002;22:415–420.

14 Prieto G, Polanco I, Sarria J, Larrauri J, Lassaletta L: Association of juvenile and adenomatous polyposis with pulmonary arteriovenous malformation and hypertrophic osteoarthropathy. J Pediatr Gastroenterol Nutr 1990;11:133–137.

15 Baert AL, Casteels-Van Daele M, Broeckx J, Wijndaele L, Wilms G, Eggermont E: Generalized juvenile polyposis with pulmonary arteriovenous malformations and hypertrophic osteoarthropathy. AJR Am J Roentgenol 1983;141:661–662.

16 Simpson EL, Dalinka MK: Association of hypertrophic osteoarthropathy with gastrointestinal polyposis. AJR Am J Roentgenol 1985;144:983–984.

17 Staalman CR, Umans U: Hypertrophic osteoarthropathy in childhood malignancy. Med Pediatr Oncol 1993;21:676–679.

18 Liu Z, Wang X, Lu Y, et al: Expression of 15-PGDH is downregulated by COX-2 in gastric cancer. Carcinogenesis 2008;29:1219–1227.

19 Li M, Xie J, Cheng L, et al: Suppression of invasive properties of colorectal carcinoma SW480 cells by 15-hydroxyprostaglandin dehydrogenase gene. Cancer Invest 2008;26:905–912.

20 Lam SK, Hui WK, Ho J, et al: Pachydermoperiostosis, hypertrophic gastropathy, and peptic ulcer. Gastroenterology 1983;84:834–839.

21 Tanaka H, Maehama S, Imanaka F, et al: Pachydermoperiostosis with myelofibrosis and anemia: report of a case of anemia of multifactorial causes and its improvement with steroid pulse and iron therapy. Jpn J Med 1991;30:73–80.

22 Pignone A, Calabro A, Rotter J: Gastric abnormalities in pachydermoperiostosis. Clin Exp Rheumatol 1992;10:72.

23 Cooper RG, Freemont AJ, Riley M, Holt PJL, Anderson DC, Jayson MIV: Bone abnormalities and severe arthritis in pachydermoperiostosis. Ann Rheum Dis 1992;51:416–419.

24 Seung-Chul L, Hong-Joo M, Deok C, et al: Pachydermoperiostosis with cutaneous squamous cell carcinoma. Int J Derm 1998;37:687–700.

25 Lakshmi TS, Rao PN, Nagaria M: Primary pachydermoperiostosis associated with Menetrier's disease. Indian J Dermatol Venereol Leprol 2001;67:256–258.

Case Rep Gastroenterol 2011;5:508–515
DOI: 10.1159/000326955
Published online: September 3, 2011

ISSN 1662–0631
www.karger.com/crg

26 Okten A, Mungan I, Kalyoncu M, Orbak Z: Two cases with pachydermoperiostosis and discussion of tamoxifen citrate treatment for arthralgia. Clin Rheumatol 2007;26:8–11.

27 Rodríguez NG, Ibáñez Ruán J, González Pérez M: Osteoartropatía hipertrófica primaria (paquidermoperiostosis). Aportación de 2 casos familiares y revisión de la literatura. Reumat Clin 2009;5:259–263.