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EDITORIAL

Important of case-reports/series, in rare diseases: Using neuroendocrine tumors as an example

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Core tip: A review of neuroendocrine tumors, which are rare diseases, strongly supports the prominent role and value of reporting of rare cases or small case series in uncommon disorders.

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Abstract

At present the publishing of case reports or case series involving small numbers of cases is controversial. While in the past they were commonly published by most journals, recently a number of prominent journals have either stopped publishing them or markedly reduced the numbers published. However, recently an increasing case is being made for their value and a number of new journals have been started devoted specifically to their publication. One of the arguments used for their value is their prominent role in rare diseases either in their recognition, full description or development of treatments. However this aspect has not been specifically studied. In this editorial this aspect is specifically examined using their role in neuroendocrine tumors as an example. Furthermore, the background of the controversy is briefly reviewed to better understand the context of this editorial.

Case reports (1 patient) or case series (> 1 patient) reporting are not without controversy: held in high regard by some[1-4] and looked down on by others as occupying the lowest rung in the evidence pyramid hierarchy[5-10]. It is necessary to understand a little more of this controversy to understand why this editorial is being written, which will be covered briefly in the next paragraph. The purpose of this editorial is to demonstrate, how in the case of an uncommon disease, such as clinically important gastrointestinal (GI) neuroendocrine tumors [carcinoids (incidence-7-13 cases/million per year) and pancreatic neuroendocrine tumors (pNETs) (incidence-1-5 cases/million per year)][11,12], case reports and case series reports have played, and are still playing, a vital and essential role in their recognition and also management/treatment.

Case or case series reports are controversial because an increasing number of prominent journals, starting in the 1980's no longer regularly published them[9,13,14]. In a survey in 1979[15] of three prominent medical journals (NEJM, JAMA, Lancet) of articles published between 1946-1974, the frequency of case reports/series (< 10 patients) remained unchanged, at 38% of all articles.

However, analyzing the same journals from 1971-1991[14], found that case reports/series frequency, as a percentage of all articles, decreased 86% from 30% to 4% of all articles, replaced by an increase in primarily clinical trials and other evidence based medicine (EBM) reports [randomized clinical trials (RCT), *etc.*]. In another study in 2006[16] of 25 journals covering various aspect of medicine, only 32% regularly published case reports/series and 33% never published them. Furthermore, other publications including areas as diverse as psychiatry and anesthesia, found that journals prominent in their field, either stopping reporting case reports/series or only infrequently published them[5,9,10,13]. This change in policy is generally attributed primarily to two factors: a general conclusion that case reports/series represent a lower level of evidence [compared to randomized clinical trials (RCT), systematic reviews, meta-analyses, cohort studies, case control studies][6,10] and the rise of the importance of impact factors (IF)[6,10].

In general case reports/series are ranked as providing one of the lowest levels (Level 3) in the evidence based hierarchy[2,6,9,10]. They have a denominator of only one (or a small number); the results can not be used for predictive value, and they can be notoriously affected by publication bias[6,10,17,18]. For example, one study[17] demonstrated in a review of case reports/series, successes were reported in 90% and failures in only 10%. It has been stated that nearly all discarded once-popular therapies were likely supported by a series of favorable cases[18]. Over the last few years, the impact factor of journals (which is determined by the citation rate) is assuming increasing importance. This is occurring because, not only is it widely used as a measure of a journal's quality, which can not only have an economic influence on the journal and the quality of the papers submitted, but also have an affect on authors, because it is increasingly used in assessing an individual's academic credentials in terms of assessing quality of publications for possible placement, promotion or other advancement[6,9,10]. The problem here is that case reports/series are generally cited less than evidence-based medicine (EBM) articles with the result they can decrease the IF of the journal[2,6,8-10,19]. This is well shown in a 2005 study[8] comparing the impact factor of various types of articles (2646 articles published in 1991, 2001). This study[8] showed case reports were the most poorly cited compared to EBM studies (meta-analysis, RCTs, epidemiological studies, case control studies). Similar results were found in a study assessing the citation rate in 2008 of papers published in *Am J Medical Genetics*, Part A in 2006, which found that the non-citation rate was 2.3 fold higher in the case reports/series than in EBM articles, and the citation rate in the case reports/series was not > 6 citations for any article, whereas in the EBM articles, many had rates higher than this.

While the presence of these negative factors discussed above, might be assumed to be leaving the case report/series in its terminal throes, in the last few years an increasing argument in their defense has been made by many[1-3,6,7,17,19-21] and for its restoration, as a prominent and useful medical reporting method. This is evidenced by both the recent appearance of numerous publications devoted to case reports/series such as the *World J of Clinical Cases*, as well as the re-institution of the case report/series format in some prominent journals[19,20,22]. One study[17] assessed one aspect of the re-inclusion of case reports into the journal Lancet[20] by studying the impact of case reports/series of innovative treatments reported in 1995/1996. This approach was taken because it is recognized that for a clinical study to be funded, evidence must be provide that proposed treatments may have merit, and case reports/series are often the first line of such evidence[17]. Of the 64 cases reports and 39 case series identified, it was found the cases were clearly read because they had an average citation rate of 17 times (range 0-336), and they also affect subsequent approaches because 22% of the cases lead to followup trials (9%-controlled trials)[17]. Other important points raised in their defense include that case reports/series: have a long tradition in teaching in medicine; they often report and establish the cause of various disorders with few observations; they provide the clinical foundation for postulating the possible pathogenesis of disorders; for therapies they are often the first evidence of the effectiveness of a new therapy, as well as often the major source of initially reporting adverse effects of different therapies; are an important teaching, education and career vehicle for young physicians (students, residents, fellows, starting faculty) to publish and contribute to the medical literature; and are important in recognizing new diseases, particularly in the case of rare diseases or rare variations of more common diseases[2,6,10,17,19,21-23]. While numerous articles have mentioned the importance of case reports/series reporting in rare diseases, this point has not been specifically examined and emphasized. It occurred to us that the study of GI-NETs (carcinoids, pNETs) offers a very good example of this assertion and thus will be briefly reviewed here and in Table 1.

Both GI- carcinoids and pNETs are classified as neuroendocrine tumors (NETs)[24-26] and although they have a different pathogenesis, they share similar histological features, aspects of their biological behavior, and many features of their management including localization methods, treatment approaches, and their abilities to be associated with hormonal-excess states due to ectopic production of biologically active substances[24,25,27-29]. There are 10 well-established pNET syndromes of which 9 are associated with specific hormone excess syndromes [Gastrinomas; insulinomas; VIPomas; glucagonomas; somatostatinomas; GRFomas; pancreatic ACTHomas; pNETs causing carcinoid syndrome, or hypercalcemia and nonfunctional pNETs (NF-pNETs)][11,26]. In addition to these 10 established pNET syndromes there are 5 other very rare (< 5 cases reported) syndromes associated with pNETs[26], which also likely represent a functional pNET syndrome. These include: pNETs secreting erythropoietin causing erythroblastosis[30]; pNETs secreting

Table 1 Sentinel case reports/series defining syndromes of disease aspects in patients with gastrointestinal neuroendocrine tumors

Year	Author	Pt#	Type of report	Syndrome	Importance	Ref.
1890	Ranson	1	Case report	Carcinoid	First description of ileal carcinoid	[50]
1902	Nichols	1	Case report	Insulinoma	First islet tumor	[49]
1922	Banting *et al*	7	Case report	Insulin treatment diabetes	Extracted insulin and effectiveness of insulin therapy in diabetes mellitus demonstrated.	[51]
1924	Harris *et al*	3	Case report	Insulinoma	1st postulate the possibility of insulinoma in his patients	[37]
1927	Wilder *et al*	1	Case report	Insulinoma	1st pNET syndrome (insulinoma). Extracting insulin from malignant pNET operated by WJ Mayo	[62]
1938	Whipple	Case review	Case review	Insulinoma	Diagnostic triad for insulinoma proposed	[52]
1942	Becker *et al*	2	Case report	Glucagonoma	First description of Glucagonoma in a patient with skin rash later found to have pNET	[38]
1950	Del Castillo *et al*	1	Case report	Cushing syndrome	First pNET associated with Cushing syndrome	[39]
1954	Thorson *et al*	16	Case series review	Carcinoid syndrome	First described a series of patients with small intestinal carcinoids, establishing the clinical entity "carcinoid syndrome"	[48]
1955	Zollinger *et al*	2	Case report	ZES	First description of ZES (gastrinoma)	[40]
1957	Priest *et al*	1	Case report	VIPoma	Recognition of WDHA syndrome (VIPoma) with pNET	[41]
1958	Verner *et al*	2	Case report	VIPoma	First complete description of all features WDHA from review/2 personal cases and 7 literature cases	[63]
1966	McGavran *et al*	1	Case report	Glucagonoma	Reported case of pNET with hyperglucagonemia and glucose elevation	[54]
1971,3	Wilkinson	1	Case report	Glucagonoma	Proposed term "NME" to describe rash in glucagonoma.	[55,56]
1974	Mallinson *et al*	9	Case series review	Glucagonoma	Reviewed pNET secreting glucagon and called attention to their association with necrotic migratory erythema (NME)	[57]
1977	Larsson *et al*	2	Case report	Somatostatinoma	Initial case of pNET producing somatostatin with symptoms	[42]
1977	Ganda *et al*	1	Case report	Somatostatinoma	Initial case of pNET producing somatostatin with diabetes	[43]
1978	Caplan *et al*	1	Case report	GRFoma	1st case of pNET secreting growth hormone-like substance with acromegaly	[46]
1979	Krejs *et al*	1	Case report	Somatostatinoma	Clinical features of somatostatinoma syndrome described and full endocrine characterization	[44]
1982	Guillemin *et al*	1	Biochemistry	GRFoma	Isolation of growth-hormone releasing factor (GRF) from patient with acromegaly with pNET	[45]
1982	Rivier *et al*	1	Case report	GRFoma		[64]
1982	Ruddy *et al*	1	Case report	Reninoma	First description of renin secreting pancreatic tumor causing symptoms	[31]
2004	Samyn *et al*	1	Case report	EPOma	Description of pNET secreting erythropoietin with syndrome	[30]
2004	Brignardello *et al*	1	Case report	LHoma	Description of pNET secreting luteinizing hormone with syndrome	[35]
2008	Chung *et al*	1	Case report	IGF-2oma	First report of pNET secreting IGF-2 with symptoms	[33]
2012	Roberts *et al*	1	Case report	GLP-1oma	First description of pNET secreting GLP-1 causing symptoms	[32]
2013	Rehfeld *et al*	1	Case report	CCKoma	First description of CCK secreting pNET with syndrome	[47]

CCKoma: pNET secreting cholecystokinin; EPoma: pNET secreting erythropoietin; GRFoma: pNET secreting Growth Hormone Releasing Factor; IGF-1oma/IGF-2oma: pNET secreting insulin-like growth factor 1 or 2; LHoma: pNET secreting luteinizing hormone; NET: Neuroendocrine tumor: NME: Necrolytic migratory erythema (skin rash) seen in glucagonoma cases; pNET: Pancreatic neuroendocrine tumor; Reninoma: pNET secreting renin; Somatostatinoma: pNET secreting somatostatin; VIPoma: pNET secreting vasoactive intestinal peptide; WDHA: Watery diarrhea, hypokalemia and achlorhydria which are features seen in VIPoma patients; ZES: Zollinger-Ellison syndrome due to ectopic secretion of gastrin by a gastrinoma causing acid hypersecretion.

renin causing hypertension[31]; pNETs secreting GLP-1 or GLP-2 causing hypoglycemia[32,33] and pNETs secreting luteinizing hormone causing masculinization[34,35]. Although the incidence of both carcinoid tumors and pNETs is increasing, they are still classified as rare conditions[36]. Whereas gastrinoma, insulinoma and NF-pNETs are the most frequent pNETs, they still have an incidence < 2/million per year and are thus rare diseases (less 1 in 1500), whereas the other pNET syndromes are 1/10-1/100 less frequent[11,12,26,29]. The functional syndrome seen most frequently with GI-carcinoid tumors is the carcinoid syndrome, characterized by flushing, diarrhea, asthma and heart disease primarily due to ectopic release of serotonin, neurokinins and perhaps other biologically active peptides[29]. The carcinoid syndrome occurs in 5%-10% of patients with carcinoid tumors and thus is also present at < 3-5/million per year and hence is also a rare disease.

As can be seen in Table 1, case reports or case series, often involving < 5 cases, played a sentinel role in most GI-NET/pNET syndromes, usually providing the initial description of the functional syndrome or in

elucidation its full clinical manifestations. Specifically, case reports/series provided the initial description of insulinoma[37], glucagonoma[38], pNETs causing ectopic Cushing's syndrome[39], gastrinoma causing the Zollinger-Ellison syndrome[40], the VIPoma (WDHA) syndrome[41], somatostatinoma and somatostatinoma syndrome[42-44], GRFoma[45,46], pNETs secreting renin[31], pNETs secreting erythropoietin[30], pNETs secreting luteinizing hormone[35], pNET secreting IGF-2 (IGF-2oma)[33], pNETs seeing IGF-1(IGF-1oma)[32], and CCKoma[47]. The initial description of the carcinoid syndrome, seen in patients with metastatic carcinoid tumors to the liver (usually ileal-jejunal-midgut tumors) was described also in a case series[48]. The sentinel role of some case reports was recognized by naming the syndrome after the initial case description such as the Verner Morrison syndrome (VIPoma-WDHA) and the Zollinger-Ellison syndrome (gastrinoma). Some of the case reports/series played other sentinel roles. These include the first description of a pNET in a report of one patient[49]; the first description of an ileal carcinoid in one case[50]; the initial use of insulin for diabetes in a case series by Banting[51] and the initial description of the clinical triad that is commonly used, even today, to suspect the diagnosis of insulinoma[26,28,52] was in a case series review, and is now referred to as Whipple's triad after this sentinel paper[53]. Some case reports/series were not the first to report a new syndrome, but played an important role in defining the spectrum of the syndrome by describing additional features of the rare pNET syndrome. This is illustrated by case reports describing the full features of the VIPoma syndrome (diarrhea, hypokalemia, achlorhydria, hypercalcemia, not associated with peptic ulcer disease or gastric hypersecretion)[11,26], after the initial report of a nonbeta cell islet tumor (pNET) associated with large volume diarrhea causing hypokalemia[41]. Similarly additional case reports/case series after the initial description of the glucagonoma syndrome (pNET with skin rash)[38], described the association of a pNET with hyperglycemia and hyperglucagonemia[54], and emphasized its association with a characteristic skin rash, which was named necrolytic migratory erythema (NME)[55-57], and which was sufficiently distinctive to become one of the main features leading to the diagnosis of glucagonomas, even at present[11,26,28,58]. Lastly, this is also the case with the somatostatinoma syndrome which was first proposed in 1977 with the description of a somatostatin secreting pNET[42], whereas the full clinical features we generally recognize today [diabetes mellitus, cholelithiasis, steatorrhea, weight loss hypo/achlorhydria, anemia][11,26,58], were later described in another case report[44]. This latter finding, illustrates another important role of case reports/case series not only in rare disorders, but also in common disorders[2,3,10,19,21,59], by reporting an uncommon feature of a common disorder or, in our case, an additional feature of a previously described, uncommon disorder.

Another conclusion that can be drawn from the findings in pNETs illustrated in Table 1 is that case reports/series have had a prominent role in GI-NETs for longer than one century, and are still playing a prominent role. This is illustrated by the descriptions of numerous new pNET functional syndromes since 2000 (Table 1) with the most recent being a case report of a patient with a cholecystokinin secreting tumor syndrome (CCKoma)[47]. The CCKoma syndrome clinically included diarrhea, severe weight loss, advanced peptic ulcer disease, cholelithiasis, all of which can be explained by the known actions of CCK expected from the profound hyperCCKemia this patient had (1000-fold increased)[47]. At present it remains unknown whether this is a very rare syndrome, which has long evaded description, or whether it is more frequent and might be responsible for patients presenting with ZES-like feature, but with normal serum gastrin levels[47,60,61].

In conclusion, a review of the role of case reports/case series in the description and establishment of the GI-NET syndromes strongly support their importance in this rare group of diseases and supports the proposal that they can play a particularly important role in any rare disease[2,6,10,17,19,21-23]. The use of case reports/case series has not only provided many of the original descriptions of these rare GI-NET syndromes, they have provided other features leading to treatments as well as full characterization of aspects of the syndromes. Case reports/small series have been important throughout the last century in the elucidation of these rare syndromes and are as important today, as they were in the past.

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