Editorial

Advance modern medicine with clinical case reports

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Abstract: Randomized clinical trial (RCT) can fail to demonstrate the richness of individual patient characteristics. Given the unpredictable nature of medicine, a patient may present in an unusual way, have a strange new pathology, or react to a medical intervention in a manner not seen before. The publication of these novelties as case reports is a fundamental way of conveying medical knowledge. Throughout history there have been famous case studies that shaped the way we view health and disease. Case reports can have the following functions: (I) descriptions of new diseases; (II) study of mechanisms; (III) discovery new therapies; (IV) recognition of side effects; and (V) education. Before submitting a case report, it is worthwhile to refer to the Case Report Check Sheet described by Green and Johnson [2006].

Keywords: Case report; randomized clinical trial (RCT); research methods

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The evidence-based health care places randomized clinical trial (RCT) at the top of the hierarchy for clinical evidence, while case reports are at the bottom (1,2). RCT is meant for the evaluation of medical interventions in which there is uncertainty about a benefit that is in itself not striking. RCT is costly and time intensive, often limit scientists and clinicians to examining a few limited variables, and can fail to demonstrate the richness of individual patient characteristics. Given the unpredictable nature of medicine, a patient may present in an unusual way, have a strange new pathology, or react to a medical intervention in a manner not seen before. The publication of these novelties as case reports is a fundamental way of conveying medical knowledge. Throughout history there have been famous case studies that shaped the way we view health and disease.

Case reports, including a single case report, two case reports, or a case series (greater than two reported cases), have a time-honored tradition. From Hippocrates (460 B.C. to 370 B.C.), and even arguably further back since the papyrus records of ancient Egyptian medicine (c. 1600 B.C.) to modern day, physicians described interesting cases involving all specialties (3). Published case reports describe important scientific observations that are missed or undetected in clinical trials, and provide individual clinical insights. A case report of Kaposi's sarcoma in a young homosexual man is the seminal observation to the finding of acquired immune deficiency syndrome (4). In 1817 James Parkinson reported an article with the title "An essay on the shaking palsy", which lead to the discovery of the disease carrying the author's name (Parkinson's disease) (5). Case reports linked the anorexic agents, fenfluramine and dexfenfluramine, with primary pulmonary hypertension and subsequently initiated trials that investigated the mechanism and incidence of this adverse effect, finally lead to their withdrawal from the market (6,7). One recent example is the publication of a case series during the outbreak of Shiga-toxin producing *Escherichia coli*, a type of enterohemorrhagic E. coli, in Germany in mid-2011 (8). Hemolytic-uremic syndrome is a severe condition commonly associated with *Escherichia coli*. It is characterized by hemolytic anemia, thrombocytopenia, acute renal failure, and is often deadly. At the start of the outbreak, a timely case series reported dramatic resolution of symptoms of *Escherichia coli* associated hemolytic-uremic syndrome after treatment with monoclonal antibody Eculizumab (9). This case series led to the rapid adoption of Eculizumab as a treatment option. In 1985, the

American Medical Association reprinted 51 papers from the Journal of the American Medical Association that had significantly changed the science and practice of medicine during the 150 years of the organization's existence. Five of these papers were case reports (10).

Case reports the following functions (11).

(I) Descriptions of new diseases: a series of cases can bring a potentially new disease to the attention of the medical public (12). The commonest variety is a further subdivision and refinement of existing entities (12). Although the AIDS virus may be over one hundred years old in central Africa, the disease was recognized only when it spread internationally. The recognition was by clinicians who were startled by the 'total immunodeficiency' in patients with no apparent reason for immunodeficiency of that type and severity (13).

(II) Study of mechanisms: clues to etiology can be derived from case reports. The first clues about tobacco smoking and lung cancer came from surgical patient series in the 1920s and 1930s; formal case-control and cohort studies came only decades later (14). A new form of thrombophilia was detected via the clotting abnormality in one family; it proved to be the most widespread genetic cause of thrombosis (15,16). Most of the recent progress in genetics, e.g., the elucidation of the genetics of cystic fibrosis or of sickle cell anaemia is also rooted in earlier case studies (17).

(III) Device new therapies: sometimes the effect of a drug is too strong against the background knowledge of usual prognosis of a patient's disease. That happened with a new therapy for chloroquine poisoning (mechanical ventilation and diazepam plus adrenaline). Ten of eleven patients survived a dose of chloroquine (5 g or more) that was quite securely known to be lethal (18). Case reports can also give clues about new indications for old drugs. Mood improvement on a tuberculostatic drug led to new antidepressants; and decreased serum cholesterol was observed in schizophrenia patients treated with niacin (19).

(IV) Recognition of side effects: side effects are sometimes detected because they produce diseases that were previously non-existent or unrecognized, for example, the eosinophilia myalgia syndrome, specific forms of valvulopathy with slimming drugs, or retrolental fibroplasia. At other times a known disease develops in unusual and unexpected circumstances: a young woman developing venous thrombosis without any precipitating factors in the first weeks of taking oral contraceptives (11). The unexpected sudden deaths during or immediately after intravenous infusion of high dosages of an anti-emetic domperidone. A few such deaths were reported independently by physicians who saw no reason for the sudden intractable arrhythmias in their patients. The intravenous form was withdrawn from the market (20).

(V) Education: case histories like the lesson of the clinicopathological conference 'do not make the same mistake as I did'; when a series of cases with an unfavourable outcome is collected to see whether that outcome might have been prevented (2,11).

Charlton and Walston suggested that the use of case series might be formalized (21). After the proposal of a new theory, one might go back to review existing cases, either from the published work or from medical practice, to see whether they fit the new theory or not. In the case of our own example, by using an MR-based intervertebral disc degeneration grading system to study a cohort of 163 healthy men (mean age, 73.5 years ±4.3) and 196 healthy women (mean age, 73.2 years ±4.1), we found that elderly female subjects had more severe disc degeneration than male subjects at all lumbar levels (22). This contradicts the general perception that men are more susceptible to disc degeneration than are women a due to increased mechanical stress and physical injury. We further reviewed the published literature and found that indeed both autopsy and MRI showed in young and middle-aged subjects, disc degeneration was observed in men in the second decade of life, occurring at an earlier age than in women; the severity of aged matched disc degeneration was also greater in men (23,24). However, in a radiographic study of subjects 55 years and older, de Schepper *et al*. (25) reported disc space narrowing was more prevalent in women than men. Based on additional literature review we proposed that relative deficiency estrogen due to menopause accelerates disc degeneration, though female discs tend to have initial milder disc degeneration during young and middle age, this trend is reversed in elderly subjects, with interception occurred around the age of menopause (26). Our further epidemiological studies provided additional supportive evidences (27). In a recent example, Koene *et al*.'s paper tries to reconstruct the natural disease course and genotype-

phenotype correlations in Complex I deficiency with four new cases and 126 case reports from literature (28).

Which cases are worthwhile to be reported is a tricky question. With the increased use of evidence-based health care, new standards are expected of case reports. Case reports must be authentic cases and have some educational value along with representing at least an incremental advance in the field. Rarity of a condition usually meets the criterion of worthiness, but few have the opportunity to describe something that is completely new. Be wary of to boast it is the "first" to describe a particular phenomenon, since even the most thorough searches often fail to reveal all instances of similar cases. Also consider presenting a case if it increases awareness of a condition, suggests the proper diagnostic strategy, or demonstrates a more cost-effective approach to management. Alternatively, a case can be presented because it represents an unusual presentation of a relatively common condition. Cases that shed new light on the possible pathogenesis of a disease or an adverse effect, increase the awareness of an unusual condition, describe a rare presentation of a common condition, or identify innovative treatment and diagnostic strategies are valuable additions to the medical literature. While it is important to contribute something unique, but not if it depends on some trivial variation from previously presented cases. For example, if it is known that a certain cancer widely metastasizes, it is not worthwhile to report each new site. Similarly, drug reactions often merit a case report, but not if it is simply a report of a drug in a class whose other members are known to cause the same reaction.

Usually a case report should include the following sections (29,30):

(I) Title: The title is a summary of the abstract and should convince the reader that the topic is relevant.

(II) Abstract: key information should be summarized in the abstract as this is the part readers will likely to pay full attention.

(III) Introduction: the introduction should be followed by an explanation of why the case report is novel or merits review, and also mention how rare the case is.

(IV) Case description: this is one of the most integral sections. The case should be described in a concise and chronological order. One should usually begin with the primary complaint, then significant family, occupational, and other social history along with any significant medications taken or allergies, followed by the physical examination, starting with the vital signs presented at the examination, along with pertinent laboratory and radiological investigations and results. There should be enough detail for the reader to establish his or her own conclusions about the validity. A case report that contains detailed and relevant patient information allows the reader with a different clinical expertise to uncover idiosyncracies that are not detected or described by the author and stimulates further inquiry and commentary. The patient's progress and outcome should be described. In the meantime be sensitive to patient confidentiality.

(V) Discussion and recommendation: the discussion section aims to compare the case report with the published literature; summarize the essential features of the report. It is essential that the author's preparation for writing the manuscript include a good review of the literature. All the references cited should be critically evaluated. Review articles should not be used as good references. A table listing the pertinent facts of the cases detected from the literature review is a good method for providing extensive, detailed data in an interpretable form.

Keeping in mind the limitations of the case report, the author must be careful not to make firm judgments and sweeping recommendations based on speculation, or on limited information. Pocock and Hughes described why randomized trials that are stopped prematurely because of extremely high benefit will more often than not be on a 'random high'; the direction of the effect is true, the magnitude is indeed large, but there is the possibility that in this particular instance mere chance added an extra benefit (31). In the next trial the effect will still be there, but may be much less than in the trial that was stopped prematurely (regression to the mean phenomenon) (31). The same caution also applies for side effects. The report that OKT3 antibody treatment in a series of transplantation patients induced a surprising number of lymphoreticular disorders early in therapy contained truth, but the magnitude of the effect reflected 'bad luck' in these patients (32).

Before submitting a case report, it is worthwhile to refer to the *Case Report Check Sheet* described by Green and Johnson (*Table S1*) (29).

RCT aims for confirmatory end and a final quantification, but offer little scientific novelty. It is the 'discovery' aspect, both scientific and educational, that makes case reports and

series great fun to present. Sir William Osler, known by many as the Father of modern medicine, once stated that physicians should "always note and record the unusual. Publish it. Place it on permanent record as a short, concise note. Such communications are always of value" (33).

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Table S1 Case report check sheet

Section	Description	Present
Authorship	All authors meet the ICMJE criteria for authorship	
	Authors are listed in the order of contribution to the paper	
Patient Privacy	All identifying information has been removed from case report materials	
	Consent from to publish the case and/or officer/IRB obtained	
Title	The title is an accurate, succinct description of the case	
Abstract	The abstract is written in a structured format	
	The objective/purpose is clearly stated	
	The important parts of patient management are highlighted	
	Key outcomes are presented	
	summarizes what the case contributes to the literature	
Key words	from PubMed medical subheadings are provided	
Introduction	The purpose is clearly stated	
	The health problem and its significance is clearly stated (e.g., prevalence, incidence, morbidity, financial and social costs)	
	Definitions for pertinent terms or concepts are provided	
	Literature on this problem was reviewed in relation to diagnosis and treatment	
	The importance of the study or how it contributes to the literature is related	
Case Report	The case is described in a concise and clear manner	
	The case is presented in chronological order	
	Pertinent patient characteristics are described	
	Salient aspects of the patient's health history are clearly described	
	Positive results and significant negative results are concisely presented	
	Appropriate outcome measures were utilized for clinical measurement	
	Novel diagnostic or assessment strategies are fully described	
	References to support the validity/reliability of novel diagnostic tests are present	
	All unusual terms and patient variables are defined	
	A diagnosis is presented	
	Treatment procedures are clearly and concisely presented	
	Important outcome measures have corresponding data reported before/after care	
Discussion	The case is compared to what is known in the literature	
	Differential diagnoses are discussed	
	A rationale for the management of the patient is provided	
	Interpretations of the results are offered by the author(s)	
	The author(s) proposes a mechanism for the observed changes	
	Limitations of the study are offered	
	Suggestions for future research are made	
Conclusion	The conclusion relates to the purpose of the paper	
	New information learned from the case is summarized	
	The conclusion is approximately one paragraph in length	
Acknowledgements	Written consent from those acknowledged is obtained	

Table S1 (*continued*)

Table S1 (*continued*)

Section	Description	Present
References	The author(s) provides adequate references, avoid only refer to review papers.	
	References are prepared as per the journal instructions for authors	
Tables	Tables present data using inter-relating horizontal rows and vertical columns	
	Tables have a corresponding title	
	Tables are self-contained, needing no text to support them	
	Permission to reprint a previously published table is obtained from the publisher	
Figures	Figures are self-contained, needing no text to support them	
	Permission to reprint a previously published figure is obtained from the publisher	
	Written permission to publish photos of identifiable people is obtained	
	Figures are prepared according to the journal's instructions to authors	
General	The case is objective and devoid of unsubstantiated claims	
	The case is clearly presented, be concise, and usually 1,000-2,500 words	
	The case is prepared in accordance with the journal's instructions for authors	

For Authors to Use as a Form of Self-evaluation Prior to Submitting a Manuscript to a Journal (reproduced from Green & Johnson 2006 with slight modification).