In Defense of Case Reports and Case Series

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Case reports and case series have their own role in the progress of medical science. They permit discovery of new diseases and unexpected effects (adverse or beneficial) as well as the study of mechanisms, and they play an important role in medical education. Case reports and series have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress; they provide many new ideas in medicine. At the same time, good case reporting demands a clear focus to make explicit to the audience why a particular observation is important in the context of existing knowledge.

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Readers of the medical literature wonder whether they should still make time to read case reports and case series. How should they balance this time-honored cornerstone of the medical literature with the demands of modern evidence-based medicine? Case reports and case series have been subject to some serious questioning. It has been said that "more often than not," new ideas from case reports are not sustained on further research, that case reports contain "misleading elements" in clinical presentation, and that they do "more harm than good" by emphasizing the bizarre (1).

Many clinicians will protest that relegating case reports and case series to second-class status in the medical literature means that babies are being thrown away with the bathwater. How can we make this concern explicit and rational? Basically, by emphasizing that all types of research have their proper place (2). Evidence-based medicine is exclusively concerned with finding the best evidence for clinical decisions; for example, should we apply a particular therapy or a diagnostic test to a particular patient? Hence, a hierarchy of evidence with the randomized trial "on top" serves one purpose admirably: the final evaluation of therapies or tests, especially when their clinical value is not immediately clear-cut. Case reports and case series, however, have other aims that are equally important in the progress of medical science and education (3). These aims are a necessary complement to the aims of evidence-based medicine.

Uses of Case Reports and Case Series

A brief list of potential roles of case reports and case series is shown in the **Table**. I discuss these roles and provide recent and ongoing examples from the literature.

In the summer of 1999, the use of a case series in the recognition of a new disease was exemplified by the epidemic of West Nile encephalitis in New York City. The astute observation of a few cases in humans and free-living crows in the zoo paved the way to molecular detection of a probable class of viruses and identification of a potential transmission route (4). The epidemic was followed by the spectacular insecticide spraying of parts of the city by helicopter. Case reporting remains important for detection of side effects of drugs, whether adverse or beneficial, even in our modern age of "designer drugs" and "pharmacogenomics." Case reporting prompted most if not all of a series of recent retractions of drugs from the market, from weight reduction agents to nonsteroidal anti-inflammatory drugs (5). Conversely, two recent pharmaceutical success stories grew from the detection of unanticipated effects: Sildenafil was developed from observation of a side effect of an antihypertensive agent (6), and the observation that the nicotine withdrawal syndrome was linked to depression paved the way to the use of antidepressant drugs as smoking cessation agents (7). Such recent pharmacologic discoveries are merely a continuation of a long tradition of serendipitous drug discovery (8).

New molecular disease mechanisms continue to be discovered thanks to age-old clinical observations on disease transmission in families. A renewed look at a family tree led to the discovery of maternally inherited diabetes associated with deafness; this in turn led to further clues to the understanding of mitochondrial diseases (9, 10). Some of the more intriguing recent applications of case reports and series have resulted from application of functional imaging techniques of the brain during auditory hallucinations or sleepwalking (11, 12). The latter are examples of preplanned case-observations, in which

Table. **Potential Roles of Case Reports and Case Series**

Recognition and description of new diseases
Detection of drug side effects (adverse or beneficial)
Study of mechanisms of disease
Medical education and audit
Recognition of rare manifestations of disease

symptoms are carefully elicited to clarify disease mechanisms. An even more elaborate example was induction of vomiting in a handful of chronic carriers of *Helicobacter pylori* (13). This study has probably solved a riddle that has baffled medicine for years: how *H. pylori* is transmitted from stomach to stomach.

Teaching of the clinical recognition of rare diseases and new or rare presentations of known diseases is a separate aim of cases and case series. In problem-oriented medical education, students no longer learn diseases, signs, and symptoms by rote. But even if they did, rarities are seldomly recognized from mere recall of textbook knowledge. Physicians develop the pattern recognition necessary for rare manifestations or rare diagnoses through confrontation with real-life demonstrations or lively papers in the course of their education and professional development. Recently, we were asked to give a second opinion about a young woman with a history of recurrent superficial thrombophlebitis on the breasts and in the axilla (our opinion was sought because of the expertise in our medical school about genetic forms of venous thrombosis and the role of hormones). Several younger medical colleagues did not believe the initial diagnosis of thrombophlebitis because they did not know of such an entity until a middle-aged clinician exclaimed, "Of course, that is Mondor's disease." A quick literature search taught us that this name is often given to superficial thrombophlebitis not only on the chest wall of young women but also on sensitive parts of young men. This led to the insight that the syndrome should be taken seriously, and neither I nor my colleagues will forget about it. This event was in the spirit of the clinical grand rounds: to use case history presentations to teach junior and senior physicians alike about our continuing ignorance and about potential mistakes that we should avoid.

Surprise, Deduction, and Induction

A recent book by Milos Jenicek (6) marries the concepts of evidence-based medicine with the aims of clinical case reporting. Most rightfully, the book has a central motto: "Case reports and case series may be the 'lowest' or the 'weakest' level of evidence, but they often remain the 'first line of evidence.' This is where everything begins" (6).

One hallmark of case reporting is to recognize the unexpected. Rather than representing the bizarre, the unexpected is where discovery begins. That is true not only in clinical case reports but also when an anomaly is observed in the laboratory. The finding of the strange behavior of a clotting test in one person from a family with multiple venous thrombosis eventually led to the discovery of activated protein C resistance and, thereafter, of the most frequent genetic abnormality that leads to venous thrombosis: the factor V Leiden mutation (14).

The idea that observations can lead to scientific discovery immediately raises the thorny problem of induction versus deduction. Karl Popper, the champion of deductive reasoning, had a straightforward solution to the problem of how to incorporate "observations as the basis of scientific discovery" into his hypothetico-deductive scheme of scientific reasoning. Casual observations strike us when they are unexpected. They are therefore refutations of our previously held beliefs and will lead to new conjectures—new ideas, and new theories (15).

That is how it goes, at least sometimes. Let us continue with the example of the factor V Leiden mutation. A case series of fatal idiopathic pulmonary emboli revealed two surprises (16): First, the association of the factor V Leiden mutation with pulmonary emboli seemed to be less pronounced than its association with venous thrombosis of the legs, and second, the number of psychiatric patients with pulmonary emboli was unexpectedly large. The first of these findings had already been reported in a previous case series (17), but initially this sounded like an anomaly; are not venous thrombosis and pulmonary embolism one and the same disease? However, when the observation of a differential association of factor V Leiden with venous thrombosis of the leg and pulmonary embolism was repeatedly confirmed, it dawned on the investigators that the clots leading to the two diseases might differ from one another, which was confirmed in another case series (18). The finding of pulmonary embolism in psychiatric patients led to the rediscovery of older literature describing venous thrombosis with neuroleptic drug use. We went back to patient records and data from a previous case–control

study; the association of venous thrombosis with neuroleptic drug use was confirmed and is in line with other recent evidence (19–21).

However, there is also Pasteur's dictum about "chance favoring the prepared mind"—a preferred expression among those of us who believe in induction from observation to ideas as the basis of scientific progress. One of the finest historical examples might be the discovery of penicillin, which was far from serendipitous. Fleming was uniquely qualified to spot immediately the anomaly in the famous window-sill culture. For years, he had tried all types of potential bacteriostatic substances on bacterial cultures and was constantly on the lookout for new ones—which is why he immediately spotted and interpreted the anomaly.

The confirmation that the role of at least one genetic risk factor, the factor V Leiden mutation, differs in venous thrombosis and pulmonary embolism strikes a chord with those of us who have pondered for years about another difference: Hypertension and smoking might be risk factors for pulmonary embolism (22), but they are not clearly known to be so for venous thrombosis of the legs. This leads to the next jump in our reasoning: Should we still consider venous thrombosis of the legs and pulmonary embolism as the same disease, given that risk factors, clot formation, diagnosis, and prognosis differ? Or should we distinguish them, much like we distinguish angina pectoris from unstable angina and from myocardial infarction? To continue the Mondor disease example: Young clinical researchers who did not know about the syndrome but are always interested in the detection of genetic risk factors for disease might now be tempted to investigate whether genetic coagulation disorders also play a role in Mondor disease. That is how the use of case reports for education (that is, teaching about a rare event) blends with the use of the same case report to spark an idea about pathophysiology.

In the end, we see a constant intermingling of surprise, deduction, and induction, ignited by case reports and case series that in turn lead to new and more formal investigations. Indeed, case reports and case series do link easily with formal studies that have proper control groups (6). Presumably, that is because a case series has a "mental" or a "literature" control group that represents the expected course of disease or the rarity of a combination of occurrences (3). Further investigation often consists of making that control group explicit.

Meta-Analysis of Case Series

One can perform a meta-analysis of case reports from the literature and arrive at meaningful new conclusions (6). For example, a compilation of case reports and case series of ischemic colitis among young persons led to the idea that it seemed to be a disease of young women, elicited by oral contraceptives in particular; this idea was confirmed in a case–control study (23). The most important rule for undertaking such a meta-analysis of case reports or series is to be perfectly clear about its aims. As another example, the first case report of aplastic anemia (by Ehrlich in 1888) was in a young pregnant woman. Ever since, pregnancy has been included in the list of potential causes of aplastic anemia. A specific search of the literature revealed only one series of consecutive young women with aplastic anemia, in which the rate of pregnancy did not turn out to be particularly worrying. Although further case reports about aplastic anemia in pregnant women have been published, these were not so abundant as one would expect from the enormous number of women who have been pregnant since 1888 (24). Moreover, several case reports described neither amelioration of aplastic anemia on cessation of pregnancy nor recurrence with subsequent pregnancies. Together with this previous evidence, the collection of a new case series led to questioning of the association of pregnancy and aplastic anemia (24).

Strength of Evidence in Case Reports

Case reports and case series have high sensitivity for detecting novelty, but they might have lesser specificity for medical decision making (3). More than a decade ago, Chalmers (25) noted that there are few formal assessments of how often conclusions based on cases and case series turn out to be correct. He drew attention to a review of the number of side effect reports that were ultimately sustained: After further investigation, 35 of 47 anecdotal reports were qualified as "clearly correct" (26). Although that review stressed the importance of avoiding false alarms and offered several suggestions for further improvement, the predictive record of such unstructured observations is amazingly good. A brief search of the literature found no signs that this study has been replicated, apart from two modeling exercises showing that case reports are likely to pick up true associations,

either for rare diseases or for more common diseases with a high relative risk (27, 28). This finding matches that of a careful review on detection of occupational toxicity, from which one may formulate the "rule of four": A number of cases (say, at least four) with an underlying relative risk of at least 4.0 must be seen over a relatively short time by a single physician or agency to permit the spontaneous discovery of occupational toxicity (29). A recent example was the description of the events leading to the detection and investigation of "flock workers' lung" (30).

The actual time–space clustering leading to the detection of a disease or a risk factor might still be a "random high" superimposed on a elevated risk at baseline (3). Yet if those are the conditions that lead to spontaneous detection, anecdotal reports stand a fair chance of being true. On the other hand, the requirement for time–space clustering also means that lower relative risks, especially of more common diseases, will not be detected spontaneously and need proper epidemiologic monitoring. As implied by Chalmers (25), more formal research is needed on the uses of case reports and case series. Nevertheless, in specific instances, detection of adverse or beneficial effects by case reports and series may lead to action (3).

How To Case-Report?

There need not be antagonism between evidence-based medicine and case reporting. Evidence-based medicine has changed the face of medicine by stressing the ultimate quantitative evaluation of therapies in patients. It has thereby changed the face of case reporting. A certain type of case report will (or should) never come back: the droning recital of one case after the other as a lame excuse for an (unstructured) review of the literature. However, now is the time to restore this time-honored form of medical reasoning to its proper place. Editors and readers alike should no longer hesitate to devote time and space to some chastened form of case reporting, one that is more precise, is more focused on its primary message, is better organized and structured, and has a better appreciation of its aims (3, 6).

The most important rule for writing a good case report is to be very clear about the single message that you want to bring. You should ask yourself why, exactly, is this particular observation important? What does it teach us? Does it run counter to some particular cherished truth? If so, spell out this truth and explain the reader how and why it is contradicted. Does it strike the "prepared mind"? If so, explain what the background ideas were and how this observation fits and extends the background idea. Is it an unexpected association? Then describe what the expectation was, even if only in terms of very crude numbers. Was it an "elicited observation" to study a mechanism? Tell the reader what was elicited and why, and whether one can generalize the mechanism. Is it a rarity that would otherwise be missed? If so, state explicitly why and how it could be missed. The writer (or narrator) should lay bare his or her thought process, as crisply and pointedly as possible, because that it the only way to impress and strike a chord with the reader. It follows that the usual "IMRAD" format (Introduction, Methods, Results, and Discussion) that one sees in reports of clinical research might not always be appropriate for case reports and case series.

Last but not least, case reporting for medical education or for medical research is great fun. Like much of medical reasoning, it has a detective-like quality (31). It brings a smile of recognition, or of satisfactory understanding, to the faces of the presentator and audience. The temporary fall from favor of this classic type of medical literature may prove to have been the best remedy for its ultimate survival.

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