Chapter 8
Special Considerations

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Adverse Drug Reaction Case Reports

Whenever a patient presents with new symptoms or abnormal laboratory results, an adverse drug reaction (ADR) should be considered in the differential diagnosis. ADRs are common; it has been estimated that 3–8 % of hospitalized patients are admitted because of ADRs, and about 7 % of hospitalized patients will experience a serious ADR during their stay [1]. Most ADRs are of the type known as dose related or "augmented," in which there is an exaggerated response to the known pharmacologic action of the drug; bleeding with warfarin and orthostatic hypotension from antihypertensive drugs are examples of these common ADRs, which are seldom reportable. Non-dose related or "bizarre" ADRs, which are uncommon, not related to the known pharmacologic action of the drug, and unpredictable, are more likely to be reportable [2]. Examples of this type include anaphylaxis to penicillin, malignant hyperthermia with general anesthetics, and (on a more delayed basis) osteonecrosis of the jaw with bisphosphonates or the teratogenicity of thalidomide.

Case reports describing ADRs have a vital role in pharmacovigilance. Before a new drug is approved for general use, phase II and phase III trials assess efficacy and safety in a few hundred to a few thousand subjects. When the drug is released

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to the general population and used by tens or hundreds of thousands of patients, rare and often unanticipated adverse effects may begin to emerge. These effects can be quite severe, as for example, in the cases of troglitazone-induced liver failure and valvular heart disease associated with fenfluramine-phentermine. Case reports of ADRs are a critical part of this postmarketing surveillance – also known as phase IV trials – in which rare adverse effects that were not detected in early clinical trials can be reported and verified.

Since ADR case reports rely largely on temporal connections to support causality, a timeline (either a figure or table; see Chap. 7) should be created to show the temporal relationship between the drug and the adverse effect. A simple timeline describing the effects of two different dialyzer types on platelet counts is shown in Fig. 7.2. A more complex timeline (Fig. 8.1), created by one of my medical student co-authors, illustrates the effects of five drugs, platelet transfusions, and splenectomy on the long-term platelet counts of a patient with refractory ITP [3]. The aim of this timeline is to show how platelet counts were affected when romiplostim was held at the time of splenectomy. A large amount of information is given in a single, easy-to-understand figure. This clarifies the timeline and allows the authors to focus on interpretation, as the reader can refer back to the figure for the day-by-day details of treatment and response.

The key to writing a convincing and publishable ADR case report is to make a compelling argument for the causal relationship between the drug and the adverse effect. In addition to the timeline, this requires a discussion of differential diagnosis and possible alternative explanations, and use of a validated causality scale to support the argument, such as the Naranjo ADR Probability Scale [4], the WHO-UMC causality categories [5], or the Liverpool adverse drug reaction causality tool [6]. Because it is simple, transparent, and easy to apply, the Naranjo scale (Table 8.1) is probably the most commonly used causality scale. Naranjo adds points for previous conclusive reports of the same reaction, temporal relationships between the drug and the event, lack of alternative causes, response to challenge and dechallenge, and other objective evidence such

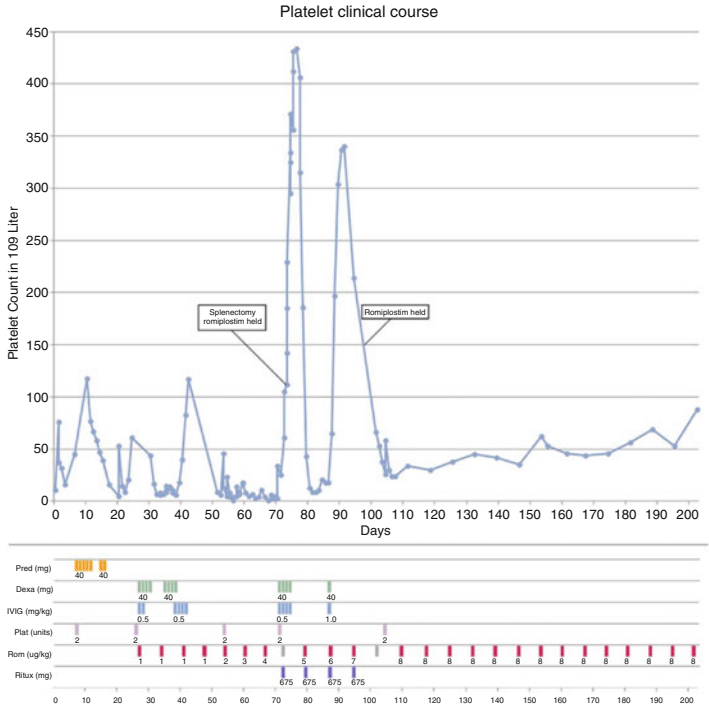

FIGURE 8.1 *Top graph* represents patient's platelet counts throughout the clinical course. *Bottom graph* represents the temporal relationship of doses of important pharmacotherapeutic agents. Each *bar* represents a single dose for a given day. Labels include drugs with the corresponding units of doses. Abbreviations: *Pred* prednisone, *Dexa* dexamethasone, *IVIG* intravenous immunoglobulin, *Plat* platelets, *Rom* romiplostim, *Ritux* rituximab (Reproduced with permission from SAGE Publications [3])

as toxic drug levels in the blood. Points are subtracted if there are alternative causes for the reaction, or if the reaction reappeared when a placebo was given. Case reports with "definite" or "probable" Naranjo scores are more likely to be published than those with "possible" scores. For drug interaction case reports, the Horn Drug Interaction Probability Scale (DIPS) has many of the same elements as the Naranjo scale, but also

Table 8.1 The Naranjo ADR probability scale

	Yes	No	Unknown	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
Did the adverse event improve when the drug was discontinued and a specific antagonist was administered?	+1	0	0	
Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
Did the reaction reappear when a placebo was given?	−1	+1	0	
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse effect confirmed by any objective evidence?	+1	0	0	

Adapted with permission from John Wiley and Sons [4]
Assessment score: Definite ≥ 9; Probable 5–8; Possible 1–4; Doubtful ≤ 0

includes questions on whether the observed interaction is consistent with the known interactive properties of both the precipitant drug and the object drug [7]. For authors who are not pharmacologists, answers to these questions will require additional research on the properties of both drugs.

In the discussion section of an ADR case report, all previous reports of the drug reaction should be reviewed and compared with the current report; causality including possible alternative explanations should be explored; and a hypothesis for the mechanism of the reaction should be proposed. The following passage gives the argument for azathioprine hypersensitivity in a patient with Crohn's disease, with recurrent fever, and concludes with the Naranjo score:

> The differential diagnosis for fever in a patient with IBD on immunosuppressive medications focuses primarily on infectious etiologies. In this patient, possible localizing clues for infection proved to be red herrings: the opacity on CXR was likely from atelectasis, and the rising bilirubin and elevated aminotransferases were due to the hypersensitivity reaction rather than biliary tree disease. In addition to the fever and leukocytosis, our patient's arthralgias and rash raised concern for extraintestinal manifestations of IBD flare. However, our patient did not have worsening intestinal IBD symptoms; moreover, he clinically improved after each "flare" without any specific intervention targeting IBD. Ultimately, it was only after the third admission with still no evidence of an infectious etiology that the possibility of AZA hypersensitivity was considered in earnest. The association became clear by aligning the timing of his fevers with the timing of AZA ingestion. Further evidence of AZA hypersensitivity included clear clinical improvement each time the AZA was stopped and the escalating clinical and laboratory manifestations that occurred with each rechallenge. This intensifying response with each exposure is a hallmark of hypersensitivity reactions. The Naranjo scale score was 8, supporting the probability that this was a true adverse drug event [8].

As another example, consider this argument in support of iatrogenic Cushing's syndrome due to an interaction between ritonavir and oral budesonide:

> Our patient developed edema, weight gain, uncontrolled hypertension, cushingoid facies, hypokalemia, and metabolic alkalosis shortly after initiation of budesonide, with resolution of all symptoms soon after it was stopped. Congestive heart failure, liver

> disease, and nephrotic syndrome were ruled out as causes of the edema, which supported iatrogenic Cushing's syndrome. Although budesonide concentrations were not measured, the very low serum cortisol level (0.8 μg/dL) in a clinical setting of hypercortisolism provides strong indirect evidence that levels of an exogenous corticosteroid (i.e., budesonide) were high. Adrenal suppression has been described in a number of cases of iatrogenic Cushing's disease due to ritonavir-steroid interactions. The Naranjo Probability Scale and Horn Drug Interaction Probability Scale score characterized this as a probable drug interaction [9].

Note that the Naranjo scale can serve as an excellent outline for the discussion section of an ADR case report. Point-by-point answers to the ten Naranjo questions (or to as many as are answerable), with full explanations for each answer, will require a full literature review and a thorough investigation of causality – which, according to the published guidelines of Kelly et al. [10], are the two essential features of an ADR case discussion.

Many ADR case reports are published, but they vary greatly in terms of quality and clinical usefulness. Several studies indicate that ADR case reports are frequently missing important elements, including route and formulation of the suspect drug, social history, weight, race, allergy history, liver and kidney function, discussion of possible mechanisms for the ADR, and use of objective rating scales to support the causal connection between drug and adverse effect [11–13]. Consequently, guidelines for submitting ADR case reports have been developed that include all relevant patient data and drug information, a full description of the adverse event, a review of previous reports in the literature, and an assessment of competing explanations and biologic plausibility [10]. All of these elements should be included in every ADR case report. Incomplete or unsubstantiated case reports are seldom published and have no role in pharmacovigilance.

N-of-1 Trials

The n-of-1 trial is a first cousin of the case report. N-of-1 trials use individual patients as study subjects, with the purpose of finding the best treatment for that individual using his or her

own data. In essence, n-of-1 trials explore variability in an objective way, and serve as a way to make individual case reports more useful and more generalizable. Some n-of-1 trials use blinding, placebo controls, crossover designs, and washout periods sequentially in a single patient [14]; others involve in-depth studies of the genomic or physiologic characteristics of a single interesting or unusual case. Although randomized controlled trials (RCTs) are generally considered the best evidence for evaluating the effectiveness of treatments or procedures, n-of-1 trials have important advantages, which are becoming increasingly clear in the era of genomic medicine and individualized treatment. Unlike RCTs, which may evaluate thousands of patients but study only a few variables, n-of-1 trials can better comprehend the myriad factors and nuances involved in a patient's response to treatment.

Any physician in active practice performs de facto n-of-1 trials every day, for example, in the selection, dosing, and titration of blood pressure medicines for a number of individual patients. Factors such as race, age, gender, comorbid conditions, renal function, medication adherence, potential side effects, financial constraints, and patient preferences all come into play. These factors are too complex to be assessed in toto by any RCT, however large and well-designed. RCTs may reveal the best treatment for a population of patients, but there are always substantial numbers of individuals who will not benefit – a state of affairs which Nicholas J. Schork has described as "imprecision medicine" [15]. The n-of-1 trial is designed to work in the opposite direction, from the particular to the general, identifying the traits of individuals and small groups of patients that would predict a favorable response to treatment. The treatment can then be generalized to larger populations of patients with the same traits, with more precision and fewer nonresponders.

There are several exciting examples of this kind of thinking in oncology, especially in the study of the small numbers of outliers who respond exceptionally well in clinical trials. In the past, these rare super-responders were dismissed as "anecdotal cases," but more recently, intensive genomic studies of these patients have revealed that specific genetic mutations, such as

the ROS1 gene rearrangement in non-small cell lung cancer and the mutated EGFR gene in colon cancer, are predictors of excellent treatment responses (to crizotinib and cetuximab, respectively). These findings are driving cancer researchers to revisit "failed" clinical trials to find and reassess more outliers [14]. In 2012, the National Cancer Institute announced the Exceptional Responders Initiative to identify and sequence the tumors from 100 extraordinary responders to any type of cancer therapy [16]. The aim is to collect and curate n-of-1 cases to create a large genomic database that can be used for clinical decision-making [17]. Conversely, reports of adverse reactions to commonly used drugs such as clopidogrel, warfarin, and carbamazepine have led to the discovery of genetic variations which can put patients at risk. This has prompted the FDA to relabel many drugs with pharmacogenomic information [18, 19]. Beyond pharmacogenomics, the use of wireless remote "phenotypic" monitoring devices – such as smartphone apps for heart rate and sleep quality, actigraphs, continuous glucose monitors, esophageal pH sensors, heart rhythm monitors, oximeters, and wrist tremor monitors for Parkinson's disease – expands the possibilities for accurate and comprehensive physiologic data collection in n-of-1 trials of treatment response [14].

What, then, is the connection between case reports and n-of-1 trials? Case reports tend to focus on the unusual – outliers, adverse drug reactions, new syndromes, atypical presentations – and often raise questions that would be best answered by n-of-1 trials. For example, there are numerous case reports of prazosin as an effective treatment for PTSD-associated nightmares; the results of randomized controlled trials have been mixed [20]. Clearly, some patients benefit, but many do not. Carefully designed n-of-1 trials, with the fullest possible accounting for the many variables in these complex patients, might reveal which patients are most likely to benefit; for those unlikely to benefit, the side effects of prazosin could be avoided. In any case report, it is important to speculate on the broader implications, including directions for future research. Therefore, the potential for n-of-1 trials (or other studies) to resolve questions raised by the case should be noted and considered in the case report discussion.

In a larger sense, case reports, like n-of-1 trials, work inductively: they go from the specific to the general. N-of-1 trials can be aggregated and subjected to meta-analysis, which can lead to valid general conclusions. Case reports are already aggregated – in a huge database, with more than 1.7 million cases indexed in PubMed – and can be used effectively for clinical decision-making when other sources of evidence are lacking.

Case Series

The case series is a group or series of observations involving patients with a similar diagnosis or cluster of symptoms, or a similar response (adverse or beneficial) to a procedure or treatment. In the epidemiology literature, the definition and design of the case series are largely neglected; in one survey of epidemiology textbooks, only five of 27 even mention case series in the index [21]. The minimum number of cases required for a case series is also unclear [22]; although some authors have argued for the "rule of four" [23], many published case series consist of only two or three cases. The case series is distinguished from case-control and cohort studies in that it lacks a comparison or control group, and does not follow patients over time using a well-defined inception point [21, 24]. This limits its statistical analysis to means, medians, ranges, and graphs, whereas case-control studies can include calculations of odds ratios and absolute risk reduction.

The aims and functions of case series are similar to those of case reports: to recognize and describe new diseases or rare manifestations of disease, detect drug side effects, study mechanisms of disease, and assist with medical education. In addition, case series are useful in case definition, clues about cause, single physician or hospital reports of outcomes, and in the development of trend or "benchmarking" analyses and multi-institutional registries [25]. Case series can offer more compelling evidence than case reports, because clusters of new or unusual cases are more convincing than isolated cases. Case series can thus function quite

persuasively as hypothesis-generating studies, which lead to additional trials for confirmation. A good example of this is the 2008 case series which showed the effectiveness of systemic propranolol in treating severe infantile hemangiomas [26]. This led to additional case series, physiologic studies, randomized controlled trials, a meta-analysis, and finally widespread acceptance of propranolol as a first-line treatment. Similarly, it was the case series of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma that led to an immune suppression hypothesis and the eventual discovery of the AIDS virus.

On the other hand, case series have their disadvantages. One major drawback is the lack of a comparison group, which makes questions of cause and effect, disease frequency, and treatment effectiveness impossible to answer without further studies. Also, case series are subject to selection bias, because the investigator self-selects the cases [27]. Because of these weaknesses, case series can cause useful treatments to be abandoned, or potentially harmful procedures to be adopted [28]. Consider the 1998 series of 12 cases by Wakefield et al. which postulated a relationship between measles, mumps, and rubella (MMR) vaccination and chronic enterocolitis and regressive developmental disorder in children [29]. This paper was found to be fraudulent and was subsequently retracted, and any connection between MMR vaccination and autism was debunked in several epidemiologic studies. However, the harm has persisted because the notion of vaccine-induced autism has gained some traction in the popular culture. This has led to reduced vaccination rates and preventable outbreaks of measles, mumps, and whooping cough over the past several years.

Although a series of cases can be collected from multiple sources, a single source may be better because it permits the use of uniform clinimetric criteria to compare and interpret the cases [25]. The authors may report only cases they have observed themselves, or assemble cases from several clinical sites. Case series can be cross-sectional studies, that is, an instant portrait of case characteristics at a set time, or longitudinal, with cases tracked as they arise over time. Longitudinal

case series give a better understanding of the clinical course and clinical outcomes [25].

When writing up a case series, the basic structure is the same as that for the traditional case report, which is discussed in detail in Chap. 7. For the majority of case series reports, which are descriptive studies involving only a few patients with no statistical testing, a "Methods" section is not required. However, in more complex case series involving large numbers of patients and statistical analysis, a brief "Methods" or "Patients and Methods" section should be added after the introduction and before the case descriptions. This should include the number of cases described, the time period and length of follow-up, inclusion and diagnostic criteria, method of assessment, description of statistical analysis, and patient consent and/or IRB approval, as required. For example, in a case series of rheumatic fever presentation and outcome in Brazil from 1986 to 2007, 178 cases were diagnosed, of which 134 were selected; inclusion criteria were age under 18 years, fulfillment of Jones criteria, and regular follow-up for at least 1 year; all cases were followed up by one author, descriptive statistics were given for continuous variables, and the probabilities of relapse and carditis were assessed with clinical and echocardiogram data and actuarial survival analysis [30].

The case descriptions should be a series of short paragraphs with all essential demographic, clinical, and clinimetric data included for easy comparison. In case series where there are too many reports to list individually, a couple of case descriptions are often included as examples, followed by a summary of all the cases with a listing of the important clinical observations. For instance, in a 1981 series of eight male homosexual patients with Kaposi's sarcoma, two brief case descriptions are given; of the group as a whole, we learn that seven had generalized lymphadenopathy, six had visceral involvement, one had possible brain involvement, three died from Kaposi's sarcoma, and one died from overwhelming cryptococcosis unresponsive to antifungal therapy. A comparison table is included with patient age, ethnic group, sites of skin and visceral lesions, CMV and hepatitis B titers, disease duration, chemotherapy, and outcome [31].

For any case series, a comparison table is essential. Unlike a single case report, where the table compares the object case with similar cases from the literature, the case series uses the table to make an internal comparison of its own cases. Table 8.2 illustrates the serum renin levels, aldosterone levels, and abdominal ultrasound findings for a series of seven Indian children with childhood Bartter's syndrome [32]. In the discussion, the authors compare the clinical and biochemical features of their patients with other case series of Bartter's syndrome in children, and note that a series of 13 Arabic children also showed hypokalemia, hypochloremia, metabolic alkalosis, and hyperreninemia in all cases. They conclude – just as in a single case report – with the important teaching points: "Bartter's syndrome should be suspected in any child with history of failure to thrive and metabolic alkalosis. Early diagnosis and treatment with NSAIDs are lifesaving."

In summary, the case series is a simple, accessible, and inexpensive way to describe new or emerging diseases, treatments,

Table 8.2 Serum renin, aldosterone, and renal ultrasound findings in seven children with childhood Bartter's syndrome

Case#	Serum renin (ng/ml/h)	Serum aldosterone (ng/l)	Ultrasound abdomen finding
1	8.5	330	Normal
2	187	848.7	Bilateral medical renal disease
3	6.05	1400	Normal
4	3.23	86.3	Bilateral mildly increased renal cortical echoes
5	8.6	752	Normal
6	40.71	967	Nephrocalcinosis
7	4	135	Normal
Mean	36.8 ± 42.3	645 ± 482.7	

Adapted with permission from Sampathkumar et al. [32]

or drug side effects, and generate hypotheses for further study. Limitations of case series include potential for selection bias, lack of a control group, lack of generalizability, and potential for harm with incorrect conclusions (the "anecdotal fallacy"). Case series follow the same basic structure as single case reports, except that a "Methods" section is sometimes needed to describe case selection and statistical analysis, and the discussion must include an internal comparison of case characteristics in addition to a review of the literature. As in any case report, the three main objectives are to place the cases in context, develop a hypothesis to explain the findings, and make a teaching point.

How to Write a "Clinical Images" Article

A good clinical image that really "tells the story" makes for a more compelling and convincing case report. I have used photographs, CT, MRI, and PET scan images, and pathology photomicrographs in my own case reports. Increasingly, real-time videos, echocardiograms, ultrasounds, phonocardiograms, angiograms, and other media are becoming the norm in the era of the online electronic case report. A good image, whether static or dynamic, can also save hundreds of words of description, which makes for a leaner and more succinct case report. Editors love to publish cases with powerful images; they also love short, concise articles. Increasingly, they are making the image the centerpiece, and shrinking the case report to a mere caption. In many journals, in fact, the "clinical images" article seems to be replacing the traditional case report. Therefore, although I shudder to consider a possible "Fahrenheit 451" future for the case report (all images, no words), I do think it is important for physicians to know how to publish their most captivating clinical images.

Contrary to many physicians' expectations, the rarest, oddest, and most extreme images are not necessarily the most publishable. In fact, a review of the "Images in Clinical Medicine" section of the *New England Journal of*

Medicine (*NEJM*) reveals a substantial number of common medical conditions (measles, rubella, myxedema, SVC syndrome) and findings (pronator drift, upper limb clonus, cannon A waves, pulsus alternans) among the oddities such as a Grynfeltt hernia, ptosis due to impacted fish mandibles over the eye of a swimmer who collided with a school of fish, and bilateral periorbital erythema migrans in a boy with disseminated Lyme disease. In its instructions for authors, *NEJM* calls for "classic images of common medical conditions," with the aim "to capture the sense of visual discovery and variety that physicians experience" [33]. This notion of "archetypal images" of common conditions is a common theme in many journals. *BMJ* is very clear about the kinds of images it does not want: "foreign bodies, results of gross trauma, poor image quality (even if interesting), simply 'textbook' presentations, very rare clinical presentations, and submissions which simply criticize other physicians, or the patient" [34]. The *Lancet* solicits visual information that will be useful to other physicians, as well as interesting, educational, and respectful of the patient; they are "less interested in pictures that simply illustrate an extreme example of a medical condition" [35]. Finally, the *Canadian Medical Association Journal* (*CMAJ*) asks for "intriguing, classic, or dramatic images" which illustrate "common presentations of rare conditions, or unusual presentations of common problems" [36]. These instructions give much latitude for various kinds of images, but the common thread seems to be that beyond amazing, amusing, and impressing us, the best clinical images should have something important to teach us. In other words, novelty is important, but so is the clinical lesson, the teaching point. In this way, clinical image articles are very much like case reports.

In general, the captions for clinical images are limited to 100–450 words, depending on the journal. The caption, according to the *Lancet*, should give a brief patient history,

put the image in context, and "explain what the image shows and why it is of interest to the general reader" [35]. This may involve further discussion of epidemiology, differential diagnosis, management strategies, prognosis, or other issues raised by the image. For example, a recent *NEJM* "Images in Clinical Medicine" article includes a video of a patient with cannon A waves, an ECG showing AV nodal re-entrant tachycardia with characteristic notching in the terminal portion of the QRS in lead V1, a brief discussion of the pathophysiology and differential diagnosis for cannon A waves, electrophysiology study results, and the clinical course including follow-up after slow pathway ablation [37]. Impressively, all of this information is conveyed in a 222-word caption. Brevity is the key with clinical images: as much as possible, let the picture speak for itself.

How does one find publishable clinical images? As Louis Pasteur said, "chance favors the prepared mind." Stay vigilant, carry a smartphone in your office and on rounds, and be prepared to request written consent before recording any patient images. Be alert not only for the unusual and bizarre, but for archetypal images of common diseases and exemplary physical exam findings. Make creative use of videos and real-time monitoring devices in addition to photographs and standard imaging studies. Use more than one modality to increase the power and persuasiveness of your images; for instance, in the case of a patient with a classic paradoxical S2 split caused by a left bundle branch block, include a phonocardiogram with respiratory tracings along with the standard 12-lead ECG. Above all, stay curious; the best reason to photograph an unexpected lesion is to preserve it, study it, and finally diagnose it. If the diagnosis is elusive, find the pathologist or dermatologist or whoever else can help you to nail it down. Like case reports, clinical images are almost never publishable without a diagnosis. Your helpful colleague will be happy to sign on as a co-author.

The "Clinical Quiz" or "Mystery Image"

Another common way to present an image is in the form of a clinical quiz, where a brief history is given in the image caption, followed by one or more questions (usually multiple choice) to test the reader's knowledge. Answers with explanations are given separately. One of my best medical students published the following clinical image article based on a patient she cared for on the wards during her internal medicine clerkship (see Fig. 8.2 and accompanying text).

Note the paradoxical title: "When Asthma is Not Asthma." If this were a simple "clinical images" article without the quiz, a straightforward title such as "Post-intubation tracheal stenosis" would be most appropriate (see my comments on case report titles in Chap. 7). However, this title is apt because a clinical quiz or mystery image works better with an ironic, mysterious, or humorous title to preserve uncertainty and entice the reader to solve the mystery.

When Asthma is Not Asthma

A 52-year-old woman with a five-pack-year smoking history was admitted to the hospital with persistent shortness of breath, wheezing, and dry cough of 2 weeks' duration following an upper respiratory infection. Her medical history was notable for a 72-hour intubation for hypoxic respiratory failure secondary to a drug overdose months prior. She had never been hospitalized for shortness of breath in the past. She was prescribed an albuterol inhaler for seasonal allergies. She is now using her albuterol inhaler four times a day with minimal relief of her symptoms. During her admission to the hospital, she was given albuterol and ipratropium nebulizers and discharged to home to complete a 5-day course of prednisone for a presumed asthma exacerbation. She returned to the emergency department 5 days later when her symptoms persisted. Lung auscultation revealed mild bilateral expiratory wheezes and stridorous breath sounds on exertion. The rest of her physical exam was unremarkable. Her chest radiograph was normal. On spirometry, her flow-volume loop demonstrated marked limitation of the inspiratory and expiratory flow, consistent with fixed obstruction. Flexible laryngoscopy revealed 80 % tracheal stenosis at the third tracheal ring. Computer tomography (CT) of the chest and neck with contrast confirmed the presence of a stenosis in the mid-trachea with an area of 6 mm by 3 mm (Fig. 8.2).

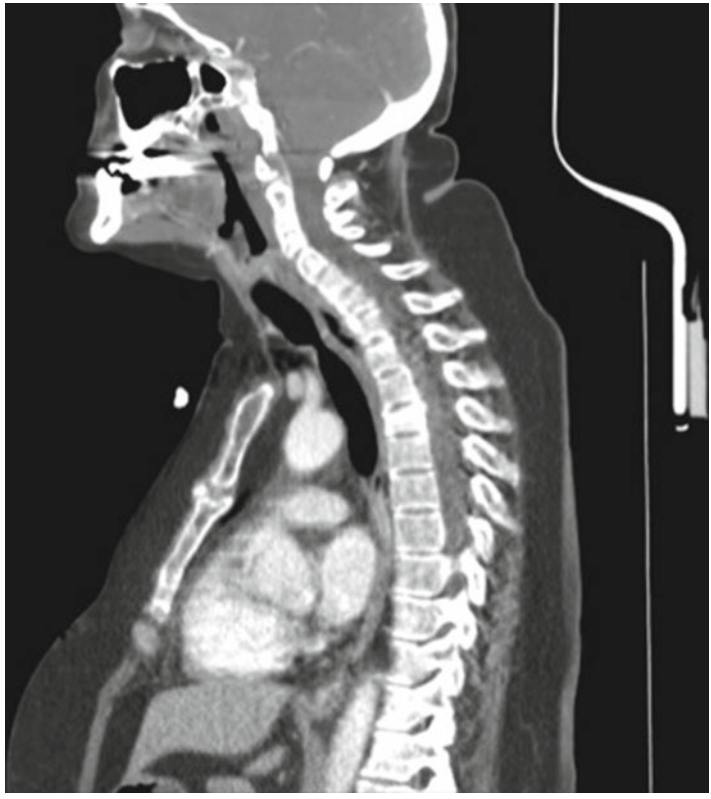

FIGURE 8.2 Sagittal CT view of the chest and neck revealing severe mid-tracheal stenosis (Reproduced with permission from Strohl and Packer [38])

What is the most significant risk factor for the development of post-intubation tracheal stenosis?

- Cuff pressure and volume
- History of GERD
- Female sex
- Concurrent use of corticosteroids
- No previous intubations

Since this is an online journal, the reader is prompted to click on the best answer. Once a selection is made, the percentage of readers who selected each answer appears:

- Cuff pressure and volume (72.31 %)
- History of GERD (15.38 %)
- Concurrent use of corticosteroids (7.69 %)
- No previous intubations (3.08 %)
- Female sex (1.54 %)

The reader is then directed to view the answer and explanation:

> Answer: A. Cuff pressure and volume
>
> MCQ Explanation:
>
> The diagnosis of tracheal stenosis should be considered in patients with a recent history of intubation who are presenting with new or worsening respiratory symptoms. It is commonly misdiagnosed as an asthma or COPD exacerbation, which results in delayed diagnosis and treatment. Cuff pressure and volume are the most significant predictors of the development of post endotracheal intubation tracheal stenosis. When stenosis develops, it most often occurs at the level of the endotracheal tube cuff. The cuff exerts pressure on the tracheal wall, leading to mucosal ischemia and ulceration, and eventual development of chondritis and fibrosis. Fortunately, the development of large-volume, low-pressure cuffs has markedly reduced the occurrence of tracheal stenosis. Other factors contributing to the development of stenosis include length of intubation, traumatic intubation, history of previous intubations, excessive corticosteroid use, advanced age, female gender, severe respiratory failure, severe reflux disease, autoimmune diseases, obstructive sleep apnea, and previous radiation therapy to the neck or chest.
>
> After diagnosis, this patient was continued on albuterol and ipratropium nebulizers and restarted prednisone with mild improvement of her symptoms. She later underwent tracheal resection with no complications [38].

Note that the typical clinical scenario, pathophysiology, risk factors, and treatment for post-intubation tracheal stenosis are all briefly discussed, and the important teaching point – that tracheal stenosis is commonly misdiagnosed as

an asthma or COPD exacerbation, which delays diagnosis and treatment – is clearly stated. The multiple-choice question is neither too difficult nor too easy, but at the appropriate level for a trainee or generalist physician reading a general medicine journal.

Subspecialty-level questions, on the other hand, should be reserved for subspecialty journals. Here is an example of a challenging multiple-choice question aimed at infectious disease specialists, which refers to a case of a pregnant woman with a multidrug-resistant KPC-producing *Klebsiella pneumoniae* pyelonephritis [39]:

Which antimicrobial(s) would be appropriate for the patient presented in the case?

A. Colistin (i.v.)
B. Oral fosfomycin
C. Oral fosfomycin and extended-infusion meropenem
D. Oral fosfomycin and extended-infusion cefepime
E. Ceftazidime-avibactam (i.v.)
F. Meropenem and ertapenem (i.v.)

The clinical image associated with this case is the genetic typing of the KPC-producing *Klebsiella* cultured from this patient, as compared with two more prevalent KPC-producing *Klebsiella* isolates. A table with antimicrobial susceptibility testing is also included. This case-based quiz provides a formidable challenge even for an infectious disease specialist, and is intended to improve care for patients with these devastating infections [40]. Similarly, the tracheal stenosis case has an important educational message for the generalist. Clinical quizzes and images help to make these teaching points more memorable, and the learning process more challenging and enjoyable.

Table 8.3 compares the features of clinical images and mystery image/clinical quiz articles. Regardless of the article type, a clear and compelling image with a strong teaching point has the best chance for publication.

Table 8.3 Comparison of clinical images and mystery image/clinical quiz articles

Article type	Clinical images	Mystery image/clinical quiz
Title	• Straightforward, descriptive	• Mysterious, ironic, paradoxical
Image Selection	• Archetypal images of common diseases/ exam findings • Rare or atypical presentations of common conditions • Classic presentations of rare conditions • Rare adverse effects • High educational value • Combine different media to enhance education (e.g., ECG and video of jugular vein pulsations) • High-quality images with appropriate legends and arrows • Avoid: foreign bodies, gross trauma, extreme rarity, poor-quality images, implied criticism of physician or patient	• In general, same as for "clinical images" articles • Diagnosable by many or most generalist physicians and some trainees • Neither too obvious nor too obscure • High educational value • High clinical relevance • Avoid: obscure and clinically irrelevant cases, trivia without clear practical value, excessive technical complexity (e.g., blots and gels, subtle radiologic variants, electrophysiologic studies) unless aimed at subspecialists

(continued)

Article type	Clinical images	Mystery image/clinical quiz
Caption	• Generally 100–450 words • Includes brief case history, discussion of pathophysiology, differential diagnosis, treatment, clinical course, implications	• Generally 300–1500 words • Brief case history only; discussion of pathophysiology, differential diagnosis, etc., given separately, following answers to multiple-choice questions
Multiple-choice questions and answers, with explanations	• N/A	• Accessible to most generalists • Subspecialty level questions only if subspecialty journal • Incorrect answers explained • Clear justification of correct answer(s), followed by full discussion
Teaching point	• Essential	• Essential

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